NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CHIESI USA, INC., *et al.*, Plaintiffs, v. **AUROBINDO PHARMA USA, INC., *et al.*,** Defendants.	Civil Action No. 19-18756 (ZNQ) (LHG) **OPINION** **(Under Temporary Seal)**

QURAISHI, District Judge

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52.

I. INTRODUCTION

Plaintiffs Chiesi USA, Inc. and Chiesi Farmaceutici S.P.A. ("Plaintiffs" or "Chiesi") bring this suit for patent infringement against Defendants Aurobindo Pharma USA, Inc. and Aurobindo Pharma Ltd. ("Defendants" or "Aurobindo"). Plaintiffs own United States Patent No. 8,658,676 ("the '676 patent"), Patent No. 10,010,537 ("the '537 patent"), and Patent No. 11,103,490 ("the '490' patent," collectively "the Patents in Suit"), which are listed in the Orange Book as covering Plaintiffs' clevidipine injectable emulsions, marketed under the brand name Cleviprex®. The Amended Complaint alleges that Defendants have infringed the Patents in Suit by filing Abbreviated New Drug Application ("ANDA") No. 213280 with the United States Food and Drug Administration.

The Court held a bench trial for 7 days, beginning on January 10, 2022, and concluding on January 20, 2022. The parties presented closing arguments and submitted proposed findings of fact and conclusions of law in April 2022.

II. JURISDICTION

This Court has subject matter jurisdiction over this action, including all claims and counterclaims asserted herein, pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

III. THE PARTIES

Plaintiff and Counterclaim Defendant Chiesi USA, Inc. ("Chiesi USA") is a corporation organized and existing under the laws of the state of Delaware, having its principal place of business in Cary, North Carolina 27518. (Final Pretrial Order, "FPO" ¶ 1) (ECF No. 298). Plaintiff Chiesi Farmaceutici S.p.A. ("Chiesi S.p.A.") (together with Chiesi USA, "Chiesi" or "Plaintiffs") is a corporation organized and existing under the laws of Italy, having its principal place of business in Parma, Italy. (FPO ¶ 2). Plaintiff Chiesi USA is a wholly owned subsidiary of Plaintiff Chiesi S.p.A. (FPO ¶ 3).

Defendant and Counterclaim Plaintiff Aurobindo Pharma USA, Inc. ("Aurobindo USA") is a corporation organized and existing under the laws of Delaware, having a principal place of business in East Windsor, New Jersey. (FPO ¶ 4). Defendant Aurobindo Pharma Ltd. ("Aurobindo Ltd.") (together with Aurobindo USA, "Aurobindo" or "Defendants") is an Indian corporation having a principal place of business in Andhra Pradesh, India. (FPO ¶ 7). Defendant Aurobindo USA is a wholly owned subsidiary of Defendant Aurobindo Ltd. (FPO ¶ 8).

IV. ISSUES FOR TRIAL

1. Have Plaintiffs proven by a preponderance of the evidence that Defendants have infringed claims 1 and/or 8 of the '676 patent, claim 7 of the '537 patent, and/or claim 6 the '490 patent?
2. Have Defendants proven by clear and convincing evidence that claims 1–8 of the '676 patent, claims 1, 2, 7 and 8 of the '537 patent, and/or claim 6 the '490 patent are invalid as obvious pursuant to 35 U.S.C. § 103?
3. Have Defendants proven by clear and convincing evidence that the '676 patent, the '537 patent, and the '490' patent are unenforceable?

V. DISCUSSION

The findings of fact herein are based on the Court's observations and credibility determinations of the witnesses who testified at trial and a thorough review of the evidence admitted at trial. While the Court has reviewed all of the evidence presented, given the length of the trial record, the Court includes references only to the evidence most pertinent to its analysis. For the reasons set forth below, the Court finds that (1) Defendants' ANDA literally infringes the claims of the Patents in Suit asserted at trial, (2) the Patents in Suit are not invalid, and (3) the Patents in Suit are not unenforceable.

A. Background of the Case

The present action is for patent infringement under 35 U.S.C. §§ 271(e)(2) and 271(a) and under the Hatch-Waxman Act, codified in part at 21 U.S.C. § 355(j). (FPO ¶ 80). Plaintiff Chiesi Farmaceutici S.p.A. is the current owner and assignee of the Patents in Suit. (FPO ¶¶ 12–13). Pursuant to 21 U.S.C. § 355(b)(1), the Patents in Suit are listed in the United States Food and Drug Administration ("FDA") publication titled *Approved Drug Products with Therapeutic Equivalence*

Evaluations ("the Orange Book") as covering Cleviprex® (clevidipine) injectable emulsions (25 mg/50 mL and 50 mg/100 mL). (FPO ¶ 15).

Plaintiff Chiesi USA, Inc. is the owner of FDA-approved New Drug Application ("NDA") No. 022156 for clevidipine injectable emulsions (25 mg/50 mL and 50 mg/100 mL), which are prescribed and sold under the trademark Cleviprex®. (FPO ¶ 53). Cleviprex is approved by the FDA for the reduction of blood pressure when oral therapy is either not feasible or not desirable. (FPO ¶ 57).

The present action arises from the submission of ANDA No. 213280 by Defendants Aurobindo Pharma USA, Inc. and Aurobindo Pharma Ltd.'s (together, "Aurobindo") seeking approval from the FDA to commercially manufacture and market generic versions of Cleviprex (clevidipine) injectable emulsions (25 mg/50 mL and 50 mg/100 mL) (the "proposed products") before the expiration of the Patents-in-Suit. (FPO ¶ 78, 81). The proposed products contain clevidipine butyrate, EDTA, oleic acid, soybean oil, glycerin, egg phospholipids, and sodium hydroxide, which is used to adjust the formulation's pH in the range of 6–8.8. (FPO ¶ 78).

Defendants counterclaim for a declaratory judgment that the Patents in Suit are not infringed (Counterclaim Count I), that they are invalid as obvious (Counterclaim Count II), are unenforceable based on inequitable conduct before the United States Patent and Trademark Office (Counterclaim Count III), and that they are unenforceable based on unclean hands (Counterclaim Count IV).[1]

[1] Defendants also moved to add certain antitrust counterclaims and to bifurcate, sever, and stay those counterclaims until after resolution of the case's principal issues of infringement, invalidity, and enforceability. *See* Defendants' Motion for Leave to File Amended Counterclaims Setting Forth Federal and State Antitrust Counterclaims, Subject to the Condition that Those Counterclaims Be Stayed and Bifurcated filed on October 8, 2021 (ECF 158). The Court severed and stayed the issue of whether to permit Defendants to add their antitrust counterclaims until after the resolution of the principal issues. *See* Letter Order entered December 6, 2021 (ECF No. 188).

At trial, Plaintiffs asserted claims 1 and 8 of the '676 Patent, claim 7 of the '537 Patent, and claim 6 of the '490 Patent against Aurobindo. (Trial Tr. at 345:17-24 (Little); Trial Tr. at 1228:5–19). Each of the Patents in Suit is presently scheduled to expire on October 10, 2031. (FPO ¶ 16). The patents are each titled "Clevidipine Emulsion Formulations Containing Antimicrobial Agents" and their specifications are substantially identical. (FPO ¶¶ 17,19). Rajeshwar Motheram and Gregory Charles Williams are listed as the named inventors on all three patents. (FPO ¶ 18).

B. Background of the Invention

The pharmaceutical formulations claimed in the Patents in Suit cover Plaintiffs' Improved Cleviprex product, [2] which contains clevidipine along with EDTA as an active antimicrobial agent and oleic acid as a stabilizing co-emulsifier. (Tr. at 107:7-22 (Motheram)); *see also, e.g.*, PTX-003 at claims; PTX-048.8). Clevidipine is a calcium channel blocker that is administered intravenously to treat high blood pressure. (Trial Tr. at 109:3-8 (Motheram)). Intravenous administration rather than oral therapy is preferred for the treatment of high blood pressure when oral delivery is not feasible or desirable, for example, in critically ill patients who are in an intensive care unit or undergoing surgery, such as a cardiac surgery where the patient may need blood pressure reduction or control. (Trial Tr. at 74:22-75:6 (Zwinski)). Improved Cleviprex has a longer period over which its vials may be used, *i.e.*, "hang time" (12 hours) compared to the previous version, Original Cleviprex (4 hours). (Trial Tr. at 84:3–85:12 (Zwinski); PTX-048.3; PTX.053.3). Improved Cleviprex was approved by the FDA in 2011. (Trial Tr. at 107:23–108:1 (Motheram)).

[2] The Court refers to the current version of the brand product at issue as "Improved Cleviprex" to distinguish it from a previous version that, as set forth below, the Court refers to as "Original Cleviprex."

C. Person of Ordinary Skill in the Art

Plaintiffs' expert, Dr. Little, opined that a POSA for the claimed inventions "is someone who has at least the equivalent of a Bachelor of Science degree in pharmaceutical sciences or chemical engineering, or an equivalent level of education or training, and several years of experience in the field of drug delivery technology or a similar field." (Trial Tr. at 342:15–25 (Little)). Aurobindo's infringement expert, Dr. Tarantino, offered a slightly different definition of the POSA, asserting that one skilled in the art has "[a] college degree in an appropriate field such as pharmacy, pharmaceutical science or chemistry, and at least four years of work experience in the field of drug formulations, including experience with emulsion and sterile formulation." (Trial Tr. 596:3–13 (Tarantino)). Aurobindo's validity expert, Dr. Crowley, offered the same definition as Dr. Tarantino. (Trial Tr. 1236:11–1237:1 (Crowley)). Dr. Tarantino opined that he disagreed with Dr. Little's definition of the POSA because "chemical engineering," in his opinion, does not "cover pharmaceutical sciences." (Trial Tr. 597:11-599:7 (Tarantino)). Dr. Tarantino did not, however, offer any support for his opinion that chemical engineers cannot or do not work in pharmaceutical sciences. (Trial Tr. at 597:11–599:7 (Tarantino)). Dr. Little asserted that chemical engineers routinely work in the pharmaceutical sciences, including his own students and his own Ph.D. advisor. (Trial Tr. at 344:4–19 (Little)). Dr. Crowley did not offer any similar criticism or discuss chemical engineering at all, nor did he testify that he disagreed with Dr. Little's proposed definition of a POSA.

The parties' proposed POSA definitions are therefore largely in agreement. The Court resolves the parties' dispute as to whether a POSA's degree could include one for chemical engineering in favor of Chiesi's position. In reaching its conclusion, the Court credits Dr. Little's uncontested testimony that his students and his own advisor have practiced in this field.

Accordingly, the Court finds that a POSA would have a Bachelor of Science degree in pharmaceutical sciences or chemical engineering, or an equivalent level of education or training, and several years of experience in the field of drug delivery technology or a similar field.[3]

D. Infringement

In support of its infringement arguments, Chiesi proffered two experts at trial. The first was Dr. Matthew DeLisa, Ph.D, the William L. Lewis Professor of Engineering at Cornell University's School of Chemical Biomolecular Engineering and Director of Cornell's Institute of Biotechnology. (Trial Tr. 294:23–296:8 (DeLisa)). Dr. DeLisa was accepted by the Court as an expert in the field of microbiology. (Trial Tr. 300:19–301:4). Chiesi's second expert was Steven R. Little, Ph.D., the William Kepler Whiteford Endowed Professor of Chemical Engineering at the University of Pittsburgh. He is the chair of the department of chemical engineering and also a professor on the faculty of several other departments at the University, including bioengineering and pharmaceutical sciences. (Trial Tr. 336:11–16 (Little)). Dr. Little was accepted by the Court as an expert in the field of pharmaceutical sciences. (Trial Tr. 341:8–18). In rebuttal, Aurobindo proffered one expert: Ralph Tarantino, Ph.D., a pharmaceutical consultant who has been involved in the pharmaceutical industry for about 40 years. (Trial Tr. 595:13–22 (Tarantino)). Dr. Tarantino, and his company Steritech Solutions, consult in the areas of formulation development, technology transfer, manufacturing, and the preparation and evaluation of regulatory submissions. (*Id.*). Dr. Tarantino was accepted by the Court as an expert in the field of pharmaceutics. (Trial Tr. 595:17–23).

[3] The Court also notes that in Aurobindo's post-trial submission, it takes the position that which POSA definition the Court adopts is not dispositive: "[r]egardless of which definition of the level of ordinary skill in the art with regard to the patents-in-suit is applied the conclusion is the same." (Aurobindo Proposed Finding of Fact ¶ 380).

1. Infringement Law

Under 35 U.S.C. § 271(e)(2)(A), an ANDA that describes "a drug claimed in a patent" constitutes an infringing act. *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1377 (Fed. Cir. 2011). The "infringement inquiry provoked by an ANDA filing . . . is focused on a comparison of the asserted patent against the product that is likely to be sold following ANDA approval." *Alcon Rsch. Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1186 (Fed. Cir. 2014) (internal quotation marks omitted). In a bench trial, whether the ANDA infringes is a question of fact. *Vanda Pharms. Inc. v. W.-Ward Pharms. It'l Ltd.*, 887 F.3d 1117, 1125 (Fed. Cir. 2018); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). The patentee must prove by a preponderance of the evidence that every claim limitation found in the patent is also found in the ANDA product, either literally or under the doctrine of equivalents.[4] *Roche Palo Alto LLC v. Apotex, Inc.*, 531 F.3d 1372, 1377 (Fed. Cir. 2008); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir. 2003). "If any claim limitation is absent . . ., there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

2. The '676 Patent: Claim 1

Claims 1 and 8 of the '676 patent are at issue. Claim 1 is the sole independent claim. It recites:

> 1. A pharmaceutical formulation comprising
>
> (a) an effective amount of clevidipine, or a pharmaceutically acceptable salt or ester,
> (b) an antimicrobial agent, EDTA, present at about 0.001 to about 1.5% w/v,
> (c) a lipid,
> (d) an emulsifier,
> (e) a tonicity modifier, and
> (f) water

[4] In this case, Plaintiffs assert only literal infringement; they do not assert infringement under the doctrine of equivalents. (*See* Plaintiffs' Pretrial Brief § III(A), ECF No. 287 at 7–15.)

wherein the formulation is resistant to microbial growth.

Aurobindo disputes infringement as to only two limitations of claim 1. (FPO ¶¶ 77, 78, 89–92; Trial Transcript 561:6–17; PTX-807.9–807.10, 834.16). It denies the proposed product meets limitation (b) regarding EDTA. It also denies the proposed product meets "wherein the formulation is resistant to microbial growth." The Court considers the evidence as to the two disputed limitations below. Because the Court can more readily dispose of the latter dispute, it first considers Chiesi's showing as to "resistant to microbial growth."

a) Wherein clause: "resistant microbial growth"

Following a *Markman* proceeding, the Court construed the phrase "resistant to microbial growth" to mean "having a reduced propensity for microbial contamination." (ECF No. 169.) At trial, Chiesi elected not to introduce evidence of any microbial testing that it may (or may not) have conducted on the proposed product to establish that the product met this limitation. Instead, Chiesi cited assertions made by Aurobindo itself (1) in its own proposed package insert that its product "inhibit[s] the rate of growth of microorganisms, for up to 12 hours" and, (2) in its proposed container and carton labelling that the proposed product "inhibits microbial growth up to 12 hours." (PTX-834.16, 835.3; Trial Tr. 561:3–17.) Chiesi then introduced documents and testimony describing antimicrobial effectiveness tests that Aurobindo conducted on batches of its own product. This testing showed that the proposed product demonstrated no increase in microbial colony count (either bacterial or fungal) over a 12-hour period. (PTX-836.9; Trial Tr. 398:3–402:25.)

Aurobindo declined to stipulate to infringement of this limitation. However, it presented no factual or expert evidence at trial to contradict Chiesi's showing as to the proposed product's

microbial growth inhibition for twelve hours,[5] nor did it address the issue in its post-trial briefing. *See* Defendants' Proposed Findings of Fact (ECF No. 367).

On the basis of Chiesi's unrebutted evidence, the Court concludes that the accused product does inhibit microbial growth for up to 12 hours and that this equates to the product "having a reduced propensity for microbial contamination." Accordingly, the Court finds that Plaintiffs have met their burden of proof with respect to establishing that the proposed product meets this claim limitation.

b) about 0.001 to about 1.5% w/v EDTA

At *Markman*, the parties stipulated that the term "about" should be construed to mean "approximately." (ECF No. 169). They also stipulated that the proposed product contains EDTA (FPO ¶ 78). Each party separately asserted that the proposed product contains 0.0005% (w/v) EDTA. (FPO ¶ 353 of Plaintiffs' Contested Facts; ¶ 325 of Defendants' Contested Facts; Trial Tr. 357:10–15.) The parties' dispute is whether a POSA would view the proposed product's 0.0005% EDTA as falling within the claimed range. For the reasons set forth below, the Court concludes that a POSA would consider the accused 0.0005% to be within the literal range of "about 0.001 to about 1.5%."

The Federal Circuit has held that "when 'about' is used as part of a numeric range, it "avoids a strict numerical boundary to the specified parameter.'" *Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008) (citing *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995)). Extension beyond the range should be limited to what "a person having ordinary skill in the art . . . would reasonably consider 'about . . .' to encompass." *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1342 (Fed. Cir. 2018).

[5] The Court notes that it barred Defendants from entering certain evidence on this issue at trial when it granted a proper motion to preclude filed by Plaintiffs. (ECF No. 317).

At trial, Plaintiffs advanced two rationales as to why the claimed EDTA range encompasses the proposed product. As part of a "purpose/function" rationale, Plaintiffs cited decisions from the Federal Circuit that have held that defining the outer reaches of "about" in a claimed range is a matter of claim construction, but "[w]hen the claims are applied to an accused device" for the purposes of analyzing infringement, "it is a question of technologic fact whether the accused device meets a reasonable meaning of 'about' in the particular circumstances." *Modine Mfg. Co. v. U.S. Int'l Trade Comm'n*, 75 F.3d 1545, 1554 (Fed. Cir. 1996). This Court agrees, that in a case like this one where there is no narrowing claim construction based on particular intrinsic-evidence statements or actions, the general considerations set forth in *Cohesive* govern its assessment of "about." *Par Pharm. v. Hospir*a, 835 Fed. App'x. 578, 584 (Fed. Cir. 2020). The extension permitted by "about" must be tied to "the purpose of the limitation in the claimed invention—not the purpose of the invention itself." *Monsanto Tech.*, 878 F.3d at 1342. It also requires examination of whether the extension is by a "modest amount," *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556, 1562 (Fed. Cir. 1994), considering the "criticality of the [numerical limitation] to the invention," *Cohesive*, 543 F.3d at 1368, as well as the "technologic and stylistic context" of the invention, *Pall*, 66 F.3d at 1217.

Here, according to Plaintiffs, a POSA would understand that "about" expands the claimed numerical range to some degree, otherwise the term would have no meaning. (Trial Tr. 356:8–13 (Little)). To determine the degree of that expansion, the POSA would first consider the purpose that the EDTA claim limitation serves in the formulation, and then assess whether a value outside the expressly stated numeric range would serve the same purpose without affecting its fundamental properties. (Trial Tr. 356:14–19 (Little)). In this regard, Plaintiffs presented uncontradicted evidence that a POSA would understand, based on the specification and the examples of the Patents

in Suit, that the purpose of the EDTA in the patented invention in this case is to limit microbial contamination. (Trial Tr. 361:13–363:21 (Little); '676 Patent 11:44–12:38.)[6] Plaintiffs also established, and Aurobindo did not deny, that the proposed product successfully employs EDTA to accomplish the same purpose. (Trial Tr. 360:10–361:7; Aurobindo Pharmaceutical Development Report ("APDR") at 8 [PTX-838.10] and Aurobindo Quality Overall Summary at 19 [PTX-832.19]). Accordingly, the Court finds that the EDTA claim limit recited by the Patents in Suit and the EDTA in the proposed product serve the same purpose.

Plaintiffs also presented evidence that the 0.001% lower limit for EDTA is not critical to the invention. Doctor Little testified as to the absence of any indication in the intrinsic record that the 0.001% is critical.[7] (Trial Tr. 363:24–364:21). He observed that none of the examples disclosed in the Patents in Suit suggest a critical threshold because none of the example formulations failed microbial testing. (*Id.*; *see also* '676 Patent 11:44–12:38). According to Dr. Little, the prosecution history was likewise silent as to where the critical lower limit for the concentration of EDTA might be found.

[6] The Court also finds that the purpose of the lower claim limit for EDTA concentration is relatively straightforward: it ensures that EDTA appears in a formulation in sufficient quantity to perform its intended function of controlling microbial contamination. This can be readily inferred from the disclosure of the Patents in Suit; the inventors varied the quantity of EDTA only to test its antimicrobial effectiveness at different levels. *See* '676 Patent 11:46–12:38; *Par Pharm.*, 835 Fed. App'x. 578, 584 (Fed. Cir. 2020) (noting, with approval, that the trial court considered not just the purpose of the claim limitation at issue, but the purpose of the end of the numerical range at issue.) The purpose of the lower end of the claimed EDTA concentration, to the extent it may be relevant, is distinct from its criticality, discussed infra.

[7] The only testimony proffered by Dr. Tarantino regarding criticality was on Chiesi's cross examination. Doctor Tarantino admitted to stating in his claim construction declaration that "a POSA would not find in regard to the lowest percentage weight/volume of EDTA in all the asserted claims that such was critical." (Trial Tr. 654:12-15). In post-trial briefing, however, Aurobindo points out that Dr. Tarantino's statement is taken out of context. In that portion of his declaration, he was opining that because FDA had effectively approved intravenous formulations with substantially higher levels of EDTA, the lower limit of the claimed range was not critical with respect to potential patient safety concerns stemming from exposure to EDTA. (*See* August 25, 2020 Declaration of Ralph Tarantino, ¶ 80 (ECF No. 46)). Viewed in its proper context, the Court therefore finds that Dr. Tarantino's trial testimony elicited by Chiesi neither supports nor contradicts Chiesi's showing as to the criticality of 0.001% EDTA, or lack thereof.

Dr. Tarantino contradicted Dr. Little on this point by citing a portion of the '537 Patent file history to suggest that a POSA would understand that values outside the expressly stated EDTA concentrations in the claimed range are "not useful" in the claimed inventions. (Trial Tr. at 608:16–609:3). In the portion of the file history on which Dr. Tarantino relies, the inventors do state that: "examples of the claimed antimicrobial agent, lipid, emulsifier, and tonicity modifier (all of which are art recognized) as well as the amounts useful in the claimed invention are recited in paragraphs [0033] to [0037] in the specification." (PTX-005.203) Dr. Tarantino ignored, however, that the "amounts useful in the claimed invention [and] recited in . . . the specification" are expressly modified by the term "about." (See PTX-005.9 (stating that "the amount of the antimicrobial agent in the formulation will generally range from *about* 0.001 to about 1.5% w/v.") (emphasis added). In other words, contrary to Dr. Tarantino's assertions, the prosecution history would not lead a POSA to understand that values below 0.001% w/v EDTA would not be useful in the claimed formulations.

Dr. Little also testified that he had seen no extrinsic evidence showing that the inventors had tested formulations with EDTA concentrations below 0.001%. He opined that, based on the information available (or perhaps not available in this case), there was nothing extrinsic to suggest that the lower limit of 0.001% EDTA was a critical value for microbial effectiveness. Aurobindo sought to contradict this point by reference to the testimony of one of the inventors, Dr. Motheram, that he conducted experiments below the 0.001% limit. The testimony, however, was limited to the following:

> Q: Now, am I correct when you determined the concentration range for EDTA, you looked for an effect on the lower end and then moved up incrementally. Correct?
>
> Motheram: I don't remember the exact flow, but that seems right.

…

> Q: So you remember going from the lowest till you could find something, and then that's where you set your concentration levels. Correct?
>
> Motheram: Yes.

(Trial Tr. 162:6–16). Aurobindo sought no further relevant testimony on this issue, and it introduced no documents to support the notion that there might have been experiments performed by the inventors to assess the criticality of the lower EDTA limit or, more importantly, what those tests might have found. To support Aurobindo's position, such tests would have needed to show that the critical limit for EDTA was somewhere *above* Aurobindo's 0.0005% EDTA concentration. In short, the Court finds that Dr. Motheram's responses to leading questions, without more, does little to contradict Chiesi's position on criticality.

Dr. Little credibly opined in conclusion that a POSA would understand the proposed product to literally meet the "about 0.001% limitation," given that (1) Aurobindo employed its 0.0005% EDTA for the same purpose, and (2) there was no evidence to suggest that the 0.001% lower claim limit was critical. [8] Dr. Tarantino did not provide a meaningful assessment of the criticality of the 0.001% EDTA limitation.[9]

Having considered the evidence presented, the Court concludes that Chiesi has shown that in light of its purpose and the lack of criticality of the claimed lower limit of EDTA, as well as the context of the invention, a POSA would view an extension below the 0.001% lower limit to

[8] Expressed in the affirmative, the Court concludes that Chiesi has shown that in light of the lack of criticality of the claimed lower limit of EDTA, a 0.0005% extension below the 0.001% lower limit is both appropriate and a "modest amount" that is consistent with the claim term's use of the term "about." *See Par Pharm.*, 835 Fed. App'x. at 584.

[9] Dr. Tarantino did opine that the amount of EDTA in the proposed product could not be considered "equivalent" to the lower limit of the 0.001% claim because it was only half the amount and "50% is in no way equivalent to 100%." (Trial Tr. at 621:5–14). Chiesi moved to strike this testimony as outside the scope of Dr. Tarantino's expert report. (ECF No. 341). The Court is not persuaded that this particular choice of expression by Dr. Tarantino to articulate his position improperly exceeded his expert reports and will deny this portion of Chiesi's motion. The Court nevertheless found Dr. Tarantino's statement largely ineffectual, given the nature of the applicable purpose/function analysis.

0.0005% (w/v) EDTA as both "modest" and consistent with the claim term's use of the term "about."[10] *See Par Pharm.*, 835 Fed. App'x. at 584. The Court therefore finds that Chiesa has shown by a preponderance that, on the basis of a purpose/function analysis, the proposed product with its 0.0005% (w/v) EDTA literally meets the "about 0.001 to about 1.5% w/v EDTA" claim limitation.[11] Given that the Court has found that the proposed product meets each of the limitations of claim 1 of the '676 Patent, the Court concludes that it literally infringes claim 1.

3. The '676 Patent: Claim 8

Claim 8 of the '676 patent claims:

> 8. The formulation of claim 1 wherein microbial growth is delayed or retarded such that there is less than 10-fold (1 log) increase in viable microbial colonies over a 24-hour period.

At trial Chiesi presented two bases for finding that the proposed product infringes claim 8. First, it introduced evidence showing that during Aurobindo's development of its proposed product, Aurobindo subjected a batch of its product (CVD/FD00407/020) to 24-hour microbial resistance testing. (Trial Tr. 304:23–305:11 (DeLisa); see also PTX-0816). Batch No. CVD/FD00407/020 is representative of the proposed product insofar as the identity and concentration of each ingredient in the CVD/FD00407/020 batch is the same as the proposed product. (Trial Tr. at 385:14-23 (Little); compare PTX-0811.3 (formulation of CVD/FD00407/020) with PTX-0832.18 (ANDA specification)). Aurobindo's testing was to assess whether the five standard USP test microorganisms increased in Batch No.

[10] In reaching what the Court perceives as a legal conclusion with respect to the modesty of the range extension, the Court also rejects Aurobindo's argument as part of its Motion to Strike Plaintiffs' Proposed Findings of Fact and Law that Chiesi had failed to show the extension was modest.

[11] Insofar as the Court concludes that a purpose/function analysis is the appropriate one in this instance and that Plaintiffs have met their burden of establishing infringement under it, the Court does not reach Plaintiffs' alternative literal infringement theory premised upon rounding/precision that is substantially more fact-intensive. This moots Chiesi's Motion to Strike portions of Dr. Tarantino's trial testimony (ECF No. 341), as well as a portion of Aurobindo's Motion to Strike Plaintiffs' Proposed Findings of Fact and Law (ECF No. 372)

CVD/FD00407/020 over a 24-hour period. Its results showed that each of the five standard microorganisms did not increase, but instead decreased, over the 24-hour period. (Trial Tr. at 305:20-307:21 (DeLisa); see also PTX-0816). Aurobindo's emails also indicated that its product did not exhibit an increase in microbial growth over a 24-hour period based on this data. (Trial Tr. at 282:2–12, 283:4–11 (Barik); see also PTX-0813; PTX-0814; Trial Tr. at 403:22–405:16 (Little)).

Second, Chiesi also introduced evidence that Aurobindo tested exhibit batches of its own proposed product (*i.e.*, batches Aurobindo manufactured and characterized as part of its ANDA submission) for microbial resistance over a 12-hour period, but not a 24-hour period. Dr. DeLisa testified that he was able to use the 24-hour microbial resistance data from developmental Batch No. CVD/FD00407/020 to extrapolate whether these exhibit batches would also demonstrate microbial resistance at 24 hours. (Trial Tr. at 308:1–309:2 (DeLisa)). Dr. DeLisa's modeling analysis shows that, like Batch No. CVD/FD00407/020, Aurobindo's exhibit batches would not exhibit an increase, but instead would exhibit a decrease, in microbial counts over a 24-hour period. (Trial Tr. at 309:7–313:7 (DeLisa)). Based upon that data, he opined that a POSA would conclude that the proposed product would meet the 24-hour microbial resistance limitation. (Trial Tr. at 313:11–15 (DeLisa)).

For its part, Aurobindo did not present affirmative evidence that its ANDA Products would fail to meet the 24-hour microbial resistance limitation. Its experts did not address whether Aurobindo's ANDA Products would fail to meet the 24-hour microbial resistance limitation. Instead, Aurobindo's attorney cross examined Dr. DeLisa regarding whether his modeling analysis considered the "lag phase" of the five standard test microorganisms. (Trial Tr. at 323:4–325:18 (DeLisa)). Dr. DeLisa explained that a lag phase is a phenomenon that may or may not occur

shortly or immediately after inoculation of a microbe into a new environment. A characteristic of such a lag phase, if it does occur, is a period of stagnant growth. (Trial Tr. at 317:23–318:1 (DeLisa)). Dr. DeLisa further testified that he did not include the lag phase in his modeling analysis because, in Aurobindo's internal 24-hour microbial resistance testing, which was used to generate his model, there was no evidence of a lag phase. Therefore, he believed it was not necessary to include a lag phase in his modeling analysis. (Trial Tr. at 318:2-10 (DeLisa)). Aurobindo did not present any documents or testimony to the contrary and Aurobindo's experts did not address lag phase at all. Dr. DeLisa also testified that "[i]t wasn't necessary" to "perform any testing of [his] own on Aurobindo's clevidipine formulation" because both "Aurobindo's . . . internal testing of microbial resistance of the 020 batch" and his "modeling analysis" each "provided ample evidence that [Aurobindo's] clevidipine formulation meets the limitation." (Tr. at 316:6–17 (DeLisa)).

Based on the uncontradicted evidence presented, the Court finds that Chiesi has demonstrated by a preponderance of the evidence that the proposed product delays or retards microbial growth "such that there is less than 10-fold (1 log) increase in viable microbial colonies over a 24-hour period." Claim 8 of the '676 Patent is therefore literally infringed by the proposed product.

4. The '537 Patent: Claim 7

Claim 7 of the ''537 patent recites:

7. A pharmaceutical formulation comprising

(a) clevidipine butyrate, present at about 0.01 to about 1% w/v,
(b) EDTA, present at about 0.001 to about 0.1% w/v,
(c) oleic acid, present at about 0.01 to about 2.0% w/v,
(d) soybean oil, present at about 4 to about 30% w/v,
(e) purified egg yolk phospholipids, present at about 0.2 to about 2% w/v,
(f) glycerin, present at about 2 to about 3% w/v, and

(g) water, up to 100% w/v.

With respect to limitation (c), Aurobindo stipulated only that its proposed product contains oleic acid. (FPO ¶ 78). With respect to its actual concentration, Chiesi introduced uncontradicted evidence, including testimony from Aurobindo's own formulations scientist, that the proposed product contains 0.3 mg/mL or 0.03% (w/v) oleic acid. (Trial Tr. at 268:3-5 (Barik); see also PTX-0807.9; see also Tr. at 555:2-25 (Ghan); PTX-0832.18). This falls within the 0.01 to about 2.0% w/v oleic acid range claimed by claim 7. The only challenge to infringement of claim 7 that Aurobindo presented was the same challenge already rejected by the Court as to the proposed product's 0.005% w/v EDTA composition. Insofar as Plaintiffs have shown by a preponderance of the evidence that the proposed product meets all limitations of claim 7, the Court finds that the proposed product infringes claim 7 of the '537 patent.

5. The '490 Patent: Claim 6

Claim 6 of the '490 claims:

6. A pharmaceutical formulation comprising:

(a) an effective amount of clevidipine, or a pharmaceutically acceptable salt or ester, present at about 0.005 to about 1% w/v,
(b) an antimicrobial agent, present at about 0.001 to about 1.5% w/v,
(c) a lipid, present at about 2 to about 30% w/v,
(d) an emulsifier, present at about 0.2 to about 2.0% w/v,
(e) a tonicity modifier, present at about 2 to about 3% w/v,
(f) a co-emulsifier, present at about 0.01 to about 2% w/v, and
(g) water;
wherein the antimicrobial agent is a chelating agent,
wherein microbial growth is delayed or retarded such that there is less than 10-fold (1 log) increase in viable microbial colonies over a 24-hour period,
wherein said antimicrobial agent is EDTA or a salt thereof, and
wherein the co-emulsifier is oleic acid.

The parties do not dispute that EDTA is "an antimicrobial agent" within the meaning of limitation (b). As with the previous claims, the only challenges that Aurobindo raised to infringement of claim 6 of the '490 Patent were based on its proposed product's EDTA

concentration and its product's microbial growth. The Court has already found the proposed product meets these limitations. Accordingly, the Court further concludes that claim 6 of the '490 patent is literally infringed by the proposed products.

For the foregoing reasons, the Court concludes that all of the asserted claims of the Patents in Suit are infringed. Accordingly, judgment will be entered in favor of Chiesi on Counts I, II, and III of the Amended Complaint and against Defendants on Count I of their counterclaims.

E. Plaintiffs' Motion in Limine re: CN 568

Prior to taking up the parties' invalidity dispute, the Court first recognizes that Chiesi filed a motion in limine seeking to preclude Aurobindo from relying on a particular piece of prior art at trial: Chinese-language patent application publication number CN 101766568A to Li Baoqui (hereinafter "CN 568"). (ECF No. 209.) The Court reserved its decision on the motion because the parties' briefing was widely disparate and because trial loomed. (*See* Letter Order Deciding the Parties' Motions in Limine issued on January 9, 2021 at 1, ECF 301.) Chiesi's motion sought to apply §§ 102(a), (b), and (e), together with concessions made by one of Aurobindo's experts regarding the earliest date of invention supported in the record, to demonstrate that CN 568 does not qualify as prior art to the Patents in Suit and therefore should not be considered. In response, Aurobindo apparently sought to attack the propriety of a Rule 1.131 declaration filed by the inventors during prosecution of the '490 patent. With little overlap in the parties' treatment of the issue, the Court deferred the motion to trial.

In its motion in limine, Chiesi argues that CN 568 does not qualify as prior art under the applicable pre-America Invents Act versions of 35 U.S.C. §§ 102(a),(b), or (e). [12] Given its relative simplicity, the Court first addresses § 102(b). On the face of each of the Patents in Suit, they claim priority back to the filing date of U.S. Provisional Application No. 61/392,294, which was filed on October 12, 2010. (PTX-001, PTX-002, PTX-003). To qualify as prior art under § 102(b), CN 568 would have needed to be published at least one year prior to the priority date of the Patents in Suit, meaning the "critical date" under § 102(b) is October 12, 2009. CN 568, however, was published in China on July 7, 2010. Because its publication date does not precede the critical date, CN 658 cannot qualify as prior art to the Patents in Suit under § 102(b).

Next, under § 102(e) CN 568 would only qualify as prior art if it were: (1) a patent application publication "filed in the United States before the invention" or (2) an international application that has "designated the United States and was published . . . in the English language." CN 568 was not filed in the United States so (1) does not apply, nor was it filed as an international application or published in English so (2) does not apply. Accordingly, CN 568 cannot qualify as prior art under § 102(e).

To reach the merits of whether CN 568 qualifies as prior art under the final provision asserted, § 102(a), the Court resorts to the trial record because it was not clear what Aurobindo's position actually was until counsel presented it at trial. Insofar as the Court relies upon the trial record, as a procedural matter it will deny Chiesi's first motion in limine, ECF 209. Nevertheless,

[12] As Chiesi correctly notes, the America Invents Act applies only to patents with effective filing dates after March 16, 2013. The Patents in Suit were filed before this date, therefore the pre-AIA provisions of Title 35, including 35 U.S.C. § 102 apply. Although Aurobindo declined to stipulate to this fact, it appears to largely concede as much in its post-trial submissions to the Court. (*See, e.g.*, Aurobindo's Proposed Conclusion of Fact ¶289 ("All of the Patents-in-Suit were examined under pre-AIA procedures as they only contain claims with an effective filing date before March 16, 2013."); but see Aurobindo's Proposed Conclusion of Fact, footnote 1 ("Because the priority applications were filed before March 16, 2013, we understand that [Plaintiffs] are asserting pre-America Invents Act statutes apply. While there is debate concerning all claims the '537 and '490 patents are available for pre-AIA treatment, all references to 35 U.S.C. §§ 102, 103, and 112 in this section refer to the pre-AIA versions of the statutes.")

for the reasons set forth below, the Court further concludes that CN 568 does not qualify as prior art under § 102(a) and, because it does not qualify as prior art under any of the asserted sections of § 102, it therefore cannot be relied upon as such for the purposes of an obviousness analysis under § 103.

Pre-AIA § 102(a) includes as prior art any information "described in a printed publication in this or a foreign country, before the invention." "Thus, under [pre-AIA] section 102(a), a document is prior art only when published before the invention date." *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996).

Initially, "the date of the invention is presumed to be the filing date of the parent application." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). This presumption can be rebutted. Here, the parties dispute how this is properly done. At trial and in its post-trial briefing, Aurobindo attempts to heighten the showing that Chiesi must make to establish an earlier invention date. It asserts that Chiesi must either prove (1) a conception and reduction to practice before the filing date of [the prior art reference] or (2) a conception before the filing date of [the prior art reference] combined with diligence and reduction to practice after that date. (Aurobindo Proposed Findings of Law). Under both of the two routes, Aurobindo therefore insists that Chiesi must establish a date of conception.[13] Aurobindo is incorrect as a matter of law.

To overcome a reference under § 102(a) via the first route, date of conception is not required. Chiesi may merely establish that the inventors reduced the invention to practice before the asserted reference. *See* 37 CFR § 1.131(b) (An affidavit of prior invention may be filed with

[13] Aurobindo's erroneous belief that Chiesi must establish conception in addition to reduction to practice led it down a complicated path that included a challenge to the propriety of the Motheram Declaration that was submitted to the Patent Office under Rule 1.131 during prosecution and appears to have formed the basis for Aurobindo's opposition to Chiesi's first motion in limine. Because Aurobindo's legal premise is faulty, the Court does not address these issues further.

a "showing of facts . . . to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence . . . to a subsequent reduction to practice."); *see Loral Fairchild Corp. v. Matsushita Elec.*, 266 F.3d 1358, 1361 ("Because [the patentee] does not argue for conception plus diligence to establish a date of invention prior to the [prior art reference], but only reduction to practice, we address only Loral's actual reduction to practice of the invention."); *Fox Grp., Inc. v. Cree, Inc.*, 700 F.3d 1300, 1304 (2012) ("Cree needs only prove it reduced its invention to practice first or that it conceived of the invention first and was diligent in reducing it to practice."). In short, Chiesi need not establish a date of conception if it can show that the invention was reduced to practice prior to a reference's date.

Establishing actual reduction to practice is relatively straightforward: it "occurs when an inventor (1) constructs an embodiment or performs a process that meets all the limitations of the claimed invention, and (2) determines that the invention would work for its intended purpose." *Ideal Innovations, Inc. v. United States*, 20-2965, 2021WL5754818, at *4 (Fed. Cir. Dec. 3, 2021) (citing *E.I. du Pont De Nemours & Co. v. Unifrax I LLC*, 921 F.3d 1060, 1075 (Fed. Cir. 2019)). Whether an invention has actually been reduced to practice is a legal question based on subsidiary factual findings. *Id*. (citing *Taskett v. Dentlinger*, 344 F.3d 1337, 1339 (Fed. Cir. 2003)). "Testing is not itself a requisite for reduction to practice, although it may be a requisite for showing that a prototype demonstrates that an invention is suitable for its intended purpose." *Id*. at *5 (quoting *Slip Track Sys. v. MetalLite, Inc.*, 304 F.3d 1256, 1267 (Fed. Cir. 2002)).

Notably, "an inventor's testimony alone is insufficient to establish an earlier reduction to practice." *Raytheon Co. v. Sony Corp.*, 727 Fed. App'x. 662, 668 (Fed. Cir. 2018) (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169–71 (Fed. Cir. 2006)). "Instead, a party

seeking to prove an actual reduction to practice must proffer evidence corroborating that testimony." *Id.* (quoting *Medichem*, 437 F.3d 1169–71). "Sufficiency of corroboration is determined by using a 'rule of reason' analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony." *Id.* (quoting *Medichem*, 437 F.3d 1169–71).

Here, both of the inventors testified that the formulations set forth in the asserted claims were conceived of and reduced to practice by at least April 1, 2009. (Trial Tr. at 123:22–128:17 (Motheram); Trial Tr. at 779:12–19 (Williams)). This is corroborated by information contained within a document referred to by the parties as the "FDA Briefing Document" (PTX-0069). Testimony from Dr. Williams and the contents of the document establish that the FDA Briefing Document was created by Dr. Williams and submitted to the FDA ahead of a meeting to discuss the proposed new clevidipine formulation that he and Dr. Motheram had developed. (Trial Tr. at 748:25-749:19 (Williams); see also PTX-0069.1). Table 6 of the FDA Briefing Document shows the composition of the proposed new pharmaceutical formulation which includes clevidipine, EDTA (antimicrobial agent), oleic acid (co-emulsifier), soybean oil (lipid), glycerin (tonicity modifier), purified egg yolk phospholipids (emulsifier), and water. (PTX-0069.23; *see also* Trial Tr. at 125:8–126:15 (Motheram)). Based upon the testing the inventors had carried out and the data that had been generated and submitted in the FDA Briefing Document, the inventors determined that their formulation would work as intended and applied for FDA approval on the basis of that determination. (Trial Tr. at 123:22-128:17 (Motheram); *see also* PTX-0069.17-21).

Aurobindo's validity expert, Dr. Crowley, did not dispute the date of invention. (Trial Tr. at 1302:2–12 (Crowley)). Perhaps more notably, Aurobindo's own patent law expert, Dr. Linck, testified that she agreed that the earliest corroborated date of invention is April 1, 2009, and that

the FDA Briefing Document itself corroborated that invention date. (Trial Tr. at 1135:5-25 (Linck)). This was also consistent with the testimony of Plaintiffs' expert, Dr. Little, who said that the inventions were reduced to practice as of April 1, 2009. (Trial Tr. at 1597:2-1599:11 (Little)). Based upon the inventors' testimony, as corroborated by the FDA Briefing Document and by testimony from both sides' experts, the Court therefore finds that Chiesi has demonstrated that the inventors had actually reduced their invention to practice by some point prior to April 1, 2009.

A consequence of the Court's conclusion is that the CN 568 reference, which was published on July 7, 2010, cannot qualify as prior art under § 102(a) because the April 1, 2009 invention date pre-dates CN 568's publication date of July 7, 2010. CN 568 will therefore not be considered prior art for the purposes of the Court's obviousness analysis.

F. Invalidity

In support of its invalidity arguments, Aurobindo proffered as an expert at trial Dr. Michael Crowley, Ph.D., a pharmaceutical consultant and adjunct professor at the University of Texas at Austin in the College of Pharmacy. (Trial Tr. 1229: 14–16 (Crowley)). Dr. Crowley is the President of Theridian Technologies, which offers "pharmaceutical consulting and drug development, formulation development, scale-up, [and] generation of FDA regulatory documents." (Trial Tr. 1229:20–1230:1). He has approximately 30 years of experience in the fields of molecular pharmaceutics and drug delivery. (Trial Tr. 1231:4–7). Dr. Crowley was accepted by the Court as an expert in the field of pharmaceutics and, more specifically, development of parenteral formulations. (Trial Tr. 1233:25–1234:13). In rebuttal on infringement, Chiesi again proffered Dr. Little as an expert.

1. Obviousness Law

Under 35 U.S.C. § 103, a patent may not issue if its claims are obvious to a POSA in light of such prior art.[14] *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1380 (Fed. Cir. 2009). Obviousness "is a question of law based on underlying findings of fact." *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). It turns on four inquiries: "(1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations such as commercial success and satisfaction of a long-felt need." *Procter*, 566 F.3d at 994; *In re Cyclobenzaprine*, 676 F.3d at 1068; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17 (1966).

Courts must assess obviousness against the state of the art at the "time the invention was made." 35 U.S.C. § 103 (pre-AIA); *KSR*, 550 U.S. at 406. "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *Depomed, Inc. v. Actavis Elizabeth LLC*, Civ. No. 12-1358, 2014 WL 4215435, at *26 (D.N.J. Aug. 25, 2014) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). In this regard, the Federal Circuit has regularly cautioned that a "fact finder must not allow its analysis to be distorted by hind-sight bias." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019); *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000) (noting the "insidious effect" of a hindsight-driven analysis). "The inventor's own path itself never leads to a conclusion of obviousness; that is

[14] 35 U.S.C. § 102 defines what qualifies as prior art for the purposes of a § 103 obviousness analysis. The Court has already reviewed the applicable paragraphs of § 102 in the portion of this Opinion deciding Defendants' Motion in Limine as to the CN 568 reference, and so will not repeat it here.

hindsight. What matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012).

"[I]n determining obviousness, the challenger bears the burden of establishing that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Millennium Pharm., Inc. v. Sandoz Inc*., 862 F.3d 1356, 1366 (Fed. Cir. 2017 (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). The Supreme Court has clarified that this analysis is to be "expansive and flexible." *KSR, Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007); *see also Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1328 (Fed. Cir. 2009) ("Common sense has long been recognized to inform the analysis of obviousness if explained with sufficient reasoning.").

"Whether a [prior art] reference was previously considered by the PTO, the burden of proof is the same: clear and convincing evidence of invalidity." *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (citation omitted). "[T]here is no heightened burden of proof when a reference was previously considered by the PTO, and no lowered burden of proof if a defendant raises a new reference or argument during litigation." *Id.* "The burden is always the same, clear and convincing evidence." *Id*. "While the ultimate burden of proof does not change, new evidence not considered by the PTO 'may carry more weight . . . than evidence previously considered by the PTO,' and may go further toward sustaining the attacker's unchanging burden." *Id*. (interior quotation marks omitted). "[I]f the PTO did not have all material facts before it, its considered judgment may lose significant force" and the burden to persuade the finder of fact by clear and convincing evidence may, therefore, "be easier to sustain." *Id.* Instead, the fact that

references were previously before the PTO goes to the weight the court or jury might assign to the proffered evidence. *Id.*

2. Aurobindo's Evidence and Arguments re: Invalidity

Aurobindo's obviousness case is not complex: it asserts that the inventions as claimed are obvious in view of an earlier version of Cleviprex (the parties refer to this product as "Original Cleviprex"), which is prior art to the inventions. The sole difference between Original Cleviprex and the claimed inventions is that the inventions include EDTA and oleic acid. (*See* Original Cleviprex Full Prescribing Information dated 2008 at 7 (listing active ingredients and excipients), PTX-0053.7; *see also* FPO at 45.). Aurobindo contends it would have been obvious to add these two missing components to Original Cleviprex in order address what Aurobindo claims were known microbial contamination issues. (Trial Tr. 1245:23–1246:2 (Crowley); Original Cleviprex Label, PTX-004.214; '576 Patent at 1:38–39; United States Patent No. 5,714, 520 to Jones *et al.*, 2:62–64 ("Microbial contamination of parenteral fluids used in 'giving sets' of this type has been recognized as one of many causes of nosocomial infection amongst ICU patients."), DTX-027).

For a teaching in the art to add EDTA specifically, Aurobindo cites to the prior art drug product Diprivan (intravenous propofol) and Chiesi's own FDA Briefing Document, which recognized the similarity of Diprivan to improved Cleviprex when it told FDA that "[m]ore relevant comparisons include the use of EDTA (0.005%) to retard the growth in intravenous propofol [Diprivan], which is a lipid-based emulsion vehicle." (FDA Briefing Document at 30). Aurobindo also cited Dr. Williams's own testimony that Diprivan was similarly formulated as an oil-in-water emulsion "although slightly different from that of Cleviprex." (Trial Tr. 768:18–21 (Williams)). Dr. Crowley testified that he "was somewhat familiar with Diprivan during [his] work career and knew some of the details," (Trial Tr. 1257:11-12 (Crowley)) and that, upon his

initial review of the '676 patent and the '537 patent, he "immediately thought of Diprivan" (Trial Tr. 1234:19–21 (Crowley)) because of the strong similarity he perceived between the formulation of original Cleviprex and the original version Diprivan without EDTA (original Diprivan), which differed only as to the active (propofol v. clevidipine) and the amount of oil in Intralipid base, (Trial Tr. 1253:5–12 (Crowley)).

Aurobindo contends that the development path of Cleviprex parallels that of Diprivan very closely. In support, it cites "The Recent Development of Propofol (DIPRIVAN®)" by Thompson and Goodale published in 2000 ("Thompson," DTX-053), which observed that EDTA "met the predefined requirements and previously had been used clinically in an aqueous intravenous solution to treat hypercalcemia and lead poisoning and as a possible treatment for atherosclerosis." (DTX-053 at 2). Thompson further stated that "EDTA is also used as an additive in a number of other pharmaceutical products." *Id*. It disclosed that "the FDA required that the chosen additive be capable of retarding the growth of microorganisms to not greater than 10-fold within 24 hours after extrinsic microbial contamination equivalent to 'touch contamination.'" *Id*. Moreover, "EDTA as 0.005% concentration in the propofol emulsion was found to be effective against 20 microorganisms, including 7 gram positive bacteria, 10 gram negative bacteria, and 3 yeast/fungi." (DTX-053 at 3). EDTA antimicrobial activity was "based on yet another extensive clinical trial program." *Id*. Finally, Thompson reported the success of the modified Diprivan insofar as "[i]n the 4 years since the introduction of the modified formulation of propofol, clinical experience in more than 30 million US patients has shown that propofol containing EDTA has reduced the incidence of fever and infections from approximately 20 per year to essentially 0." (DTX-053 at 4). Aurobindo argues that the FDA Briefing Document makes clear that EDTA was added to Original Cleviprex for the same purpose it was added to original Diprivan. (FDA Briefing

Document at 9 ("In addition, the selected EDTA at 0.005% level is the same as that in emulsion drug product Diprivan® which has been approved for use for potential microbial retardation.")).

Aurobindo also contends it was well known in the art to add oleic acid, as recognized at two points in the FDA Briefing Document ("[o]leic acid was selected as a co-surfactant to further stabilize the emulsion because it is commonly used for this purpose" and "oleic acid is a commonly used excipient in a number of currently approved and marketed parenteral emulsions" (FDA Briefing Document at 15) and in the Pharmaceutical Development section of the sNDA filed with FDA for Improved Cleviprex ("[o]leic acid was selected because it is commonly used as a co-emulsifier in commercially available injectable lipid emulsions," PTX-800.4). Yamaguchi 1995, a reference cited by Dr. Williams in the FDA Briefing Document, conveyed how oleic acid functioned by that "Washington and Davis (5) reported that the surface negative electric potential of LE [lipid emulsion] was decreased by the addition of a fatty acid such as oleic acid." (PTX-0069.161) and therefore "oleic acid prevented flocculation and coalescence" (PTX-0069.165). Moreover, Aurobindo points to Dr. Williams' own testimony admitting that oleic acid was chosen as a co-emulsifier when instability in the formulation was noted because it was naturally found in soybean oil. (Trial Tr. 782:17–783:2 (Williams)). Dr. Crowley confirmed that oleic acid is present in both soybean oil and egg yolk phospholipids. (Trial Tr. 1353:3–6 (Crowley)).

On cross examination, however, Dr. Crowley admitted that, generally speaking, "pharmaceutics is a complex science and that a single additive can affect the entire composition taking into account not only the particular ingredient but also the amount of each ingredient." (Trial Tr. at 1346:18–22 (Crowley)). Consequently, and as Dr. Crowley agreed, "in the pharmaceutical industry a great many innovative formulations are developed from known

acceptable ingredients in the FDA [inactive ingredient database] list" and, in fact, Dr. Crowley has done this many times himself. (Tr. at 1346:23-1347:3 (Crowley)).

With respect to comparisons to Diprivan, Dr. Crowley also admitted that Diprivan's formulators were motivated to add EDTA because it was known in the art at the time that health-care providers were using improper aseptic technique (i.e., multiple sticks) with the original Diprivan formulation (without EDTA) and that the improper technique had led to contamination and clusters of infections. (Trial Tr. at 1257:5-1258:17, 1321:1-15 (Crowley)). Dr. Crowley conceded that he was not aware of any similar problems known in art with respect to Original Cleviprex. Specifically, he had not seen (1) any reports of clusters of infections with Original Cleviprex; (2) any reports of Original Cleviprex being improperly used; or (3) any reports of improper aseptic technique for Original Cleviprex. (Trial Tr. at 1321:23–1322:7 (Crowley)). Instead, if anything, experience had shown that Original Cleviprex had been used safely in clinical trials with a vial hang time of 12 hours. (Trial Tr. at 1322:8–12 (Crowley); *see also* Trial Tr. at 740:11–13 (Dr. Williams discussing 12-hour hang time safely used during the Original Cleviprex clinical trials) (Williams)).

3. Chiesi Rebuttal re: Obviousness

Chiesi's response at trial to Aurobindo's invalidity presentation was detailed and thorough.

a) References Did Not Show Inventive Combination

Chiesi first asserted that there was no disclosure of EDTA in combination with clevidipine in the prior art presented by Aurobindo. Likewise, no prior art included a teaching of oleic acid in combination with clevidipine.

b) Aurobindo Analysis as Improper Hindsight

Second, Chiesi accused Aurobindo of hindsight analysis. It faulted Aurobindo for providing Dr. Crowley with the Patents-in-Suit before he conducted his obviousness analysis.

(Trial Tr. at 1300:17–20 (Crowley)). It argues Aurobindo should have given Dr. Crowley information about the Original Cleviprex formulation first and then subsequently asked if, in the 2009 timeframe, there would have been any known problem to be solved with Original Cleviprex. (Trial Tr. at 1300:21-25 (Crowley)). It should have also given Dr. Crowley information about the Original Cleviprex formulation first and then subsequently asked what, if any, changes a POSA would have made to Original Cleviprex in the 2009 timeframe. (Trial Tr. at 1301:1-5 (Crowley)). Chiesi also faults Dr. Crowley for considering what he called "admission[s]" from the inventors, contained within the "FDA Briefing Document." (*See, e.g.,* Trial Tr. at 1264:3-1265:14 (Crowley)). According to Chiesi, these statements are not properly considered in an obviousness analysis because they were not made by a POSA or available to a POSA, but were instead made in confidential regulatory documents with hindsight after the inventions were made and tested. They argue that Dr. Crowley's testimony demonstrated the hindsight effect they had on his analysis when he admitted that "Well, I saw them and so you can't unsee them." (Trial Tr. at 1352:19–23 (Crowley)).

c) *No Motivation to Modify Original Cleviprex*

Third, Chiesi maintains that Aurobindo failed to establish, by clear and convincing evidence, that there was any known problem to be solved that would have motivated a POSA to arrive at the claimed inventions. Chiesi notes that at the time of invention, Original Cleviprex had only been recently approved in December 2008. (Trial Tr. at 79:19–80:17 (Zwinski); PTX-053 (Original Cleviprex Package Insert, dated 2008)). It did not contain EDTA or oleic acid. (*See* PTX-053.7 (Section 11"Description"); Trial Tr. at 1320:13–22 (Crowley)). And, as discussed, *supra*, Dr. Crowley recognized that unlike Diprivan, which Aurobindo relied upon as a motivation to modify Original Cleviprex, there was no evidence in the art showing contamination issues or cluster infections with Original Cleviprex. (Trial Tr. at 1257:5–1258:17, 1321:1–15 (Crowley)).

Dr. Little, Dr. Crowley, and fact witnesses were consistent on this point. (Trial Tr. at 1549:22-1550:18, 1629:21-1630:21 (Little); Tr. at 72:24-73:15, 81:17-24 (Mr. Zwinski describing his familiarity with Original Cleviprex before he joined Chiesi in 2012); Trial Tr. at 82:12–20 (Mr. Zwinski testifying that he had not heard of any microbial contamination issues, infections, or stability problems associated with the use of Original Cleviprex prior to joining Chiesi in 2012); Trial Tr. at 154:21–155:2 (Dr. Motheram confirming on cross examination that he couldn't recall any reports of cluster infections with Original Cleviprex); Trial Tr. at 741:6–25 (Dr. Williams testifying that Original Cleviprex was used in about 2,000 patients in clinical trials with a 12-hour hang time and no reports of infections)).

(1) No Motivation to Include EDTA

Chiesi also notes that Dr. Crowley testified that the approval of the Diprivan+EDTA formulation was in 1996, and the first marketing of Original Cleviprex (without EDTA) occurred in 2008. It argues the intervening 12-year period confirms the absence of any motivation because, if Diprivan had provided a motivation, as Aurobindo contends, Original Cleviprex would have been formulated with EDTA. (Trial Tr. at 1557:16–1558:13 (Little); *see also* PDX6.11; Trial Tr. at 1251:1–8, 1320:23–25 (Dr. Crowley acknowledging, on both direct and cross examination, the 12-year difference)). Dr. Little provided a rationale for why EDTA was not added to Original Cleviprex that went unrebutted by Dr. Crowley: "[T]here are a lot of formulations that are made that are single-use formulations. They're made to be sterile. So they don't have bacteria growing in them whenever they're in the bottle." (Trial Tr. at 1558:14–19 (Little)). Consequently, "[i]t is not the case that you would just assume that every single-use product that you would use would need an antimicrobial effectiveness agent, even if it's made out of the same things [i.e., Intralipid], which I don't agree with [for Original Cleviprex and Diprivan]." (Trial Tr. at 1558:22–25 (Little)).

There was evidence presented at trial by both parties' experts on this point. Dr. Crowley presented a long list of drugs (and classes of drugs) that were purportedly formulated in the same emulsion base—Intralipid. (DDX-15). Dr. Crowley confirmed that Diprivan was the sole example, out of the many drugs and classes of drugs listed, that was formulated with EDTA. (Trial Tr. at 1312:10–23 (Crowley)). Dr. Little noted that none of the references that Dr. Crowley relied upon, with the exception of Diprivan, were formulated with EDTA. (Trial Tr. at 1561:8–18 (Little)). Instead, the evidence showed that, in addition to Original Cleviprex, other drugs on DDX-15 were formulated without EDTA after Diprivan+EDTA was approved in 1996. (Trial Tr. at 1312:25-1313:18, 1314:7-1320:12 (Crowley)).

Even assuming *arguendo* that there was a known problem to be solved with Original Cleviprex, Chiesi maintains that Aurobindo did not prove, by clear and convincing evidence, that a POSA would have been motivated to add EDTA to clevidipine as an antimicrobial agent to arrive at any of the claimed inventions. EDTA was not known to be a broad-spectrum antimicrobial agent, a "major criteria," given that when selecting a preservative to be included in an injectable formulation "it should be effective against a wide spectrum of microorganisms." (Trial Tr. at 1307:21–1308:1 (Crowley)). In fact, numerous references indicated that "EDTA was known to not be a very good antimicrobial agent." (Trial Tr. at 1550:19–1551:13 1562:11–24 (Little)). Moreover, it "was specifically taught to not be a broad-spectrum antimicrobial agent and it was specifically taught to be used with other [antimicrobial agents], not by itself." For example, and as both parties' experts agreed, prior art Patent No. 5,714,520 to Jones *et al*. ("Jones '520 Patent") disclosed that EDTA "is not regarded as a broad spectrum antimicrobial agent." (DTX-027 at 4:22-37; Trial Tr. at 1310:11–21 (Crowley); Trial Tr. at 1562:25–1563:17 (Little)). And both parties' experts agreed that the Thompson reference likewise disclosed that "EDTA should not be

considered a complete antimicrobial agent because its action is dependent on bacterium as well as the medium involved." (DTX-053 at Aur_Cle-00116401; Tr. at 1310:3-10 (Crowley); Trial Tr. at 1562:25–1563:3, 1563:8–24 (Little)). In short, the prior art taught that, if a POSA were going to use EDTA as an antimicrobial agent, then it would have to be used in combination with other antimicrobial agents, not on its own. (Trial Tr. at 1551:10-13, 1564:4-25 (Little)). By way of example, both parties' experts agreed that the 2003 Handbook of Pharmaceutical Excipients ("HPE") disclosed that EDTA's antimicrobial activity "is insufficient for [it] to be used effectively as antimicrobial preservative on its own." (DTX-028 at Aur_Cle-0006964; Trial Tr. at 1333:7-1334:6 (Crowley); Tr. at 1564:4-25 (Little)). The disclosure from the HPE is significant because, as Dr. Crowley agreed, "a person of ordinary skill in the art . . . heavily relies upon the Handbook of Pharmaceutical Excipients for information about inactive ingredients," such as EDTA. (Trial Tr. at 1333:7–20 (Crowley)).

Chiesi says Aurobindo also admitted elsewhere that using EDTA alone in a clevidipine suspension of this kind was contrary to teachings in the prior art. Aurobindo's admission was made in the process of its own U.S. patent application for a clevidipine, EDTA, and oleic acid suspension when it sought to distinguish its proposed invention from the prior art. It argued to the USPTO that the "[p]rior art discloses use of antimicrobial agent which may comprise more than one different antimicrobial agents. . . . So compared to prior art [the] present invention uses only one antimicrobial agent." (PTX-864.134 (emphasis in original)).

Chiesi introduced evidence from both parties' experts and fact witnesses that there were potential safety concerns disclosed throughout the prior art with respect to using EDTA in combination with a calcium channel blocker like clevidipine. (Trial Tr. at 111:9–115:11 (Motheram); Trial Tr. at 261:24–262:3, 287:1–288:13, 289:19–290:11 (Barik); Trial Tr. at 761:12-

762:21 (Williams); Trial Tr. at 806:25–807:4 (Ding); Trial Tr. at 1333:7–1336:4 (Crowley); Trial Tr. at 1566:4–1570:2 (Little); DTX-028 at Aur_Cle-0006965; DTX-320 at CHI_CLE_0000358; PTX-802.5; PTX-803.2; PTX-819.3; PTX-864.135-136). The prior art taught that EDTA is a chelating agent and could therefore cause calcium depletion. For example, the HPE discloses that EDTA is a chelator that can "cause calcium depletion (hypocalcemia)." (DTX-028 at Aur_Cle-0006985; Trial Tr. at 1566:11-1567:4 (Little)). U.S. Patent No. 8,148,356 ("the '356 Patent") likewise discloses that EDTA is a chelating agent that can cause "undesirable effects includ[ing] a significant drop in serum calcium levels." (DTX-320 at 2:12-25; Trial Tr. at 1567:11–25 (Little)). Dr. Crowley agreed that hypocalcemia can be life threatening. (Trial Tr. at 1338:1–3 (Crowley)). Aurobindo and the applicants of the Patents in Suit relied upon hypocalcemia (and the '356 Patent specifically) to argue to the USPTO that the art would have taught away from the use of EDTA (especially with clevidipine). (Trial Tr. at 1569:23–1570:2 (Little)). In fact, Aurobindo relied on the potential for hypocalcemia—even at the EDTA concentrations present in the FDA-approved Improved Cleviprex—as the entire basis for its own clevidipine, EDTA, and oleic acid patent application. Aurobindo explicitly states in its patent application:

> Intravenous formulations using disodium EDTA can lead to [a] decline in concentration of calcium . . . . A rapid decline in blood calcium can lead to muscle spasm. It can cause severe hypocalcemia, brachiopods, bronchial spasms, seizures and even apnea. Effects on the cardiovascular system. . . can occur in severe ventricular fibrillation.
>
> Hence, there is still a need to design pharmaceutical composition[s] of clevidipine that have prolonged stability, efficacy and reduced side effects. Inventors of the present invention have endeavored to develop such formulations that are also economical and commercially viable while having none or lower concentration of antimicrobial agent [EDTA]. . . ."

(PTX-819; Trial Tr. at 1568:8–1569:10 (Little)).

Chiesi pointed to a second reason not to use EDTA in the context of the claimed inventions: the prior art cautioned against the use of EDTA in patients with impaired cardiac function. (Trial Tr. at 1566:11–1567:22 (Little)). For example, both parties' experts agreed that this is disclosed in the HPE. (DTX-028 at Aur_Cle-0006965; Trial Tr. at 1333:7-20, 1334:14-18 (Crowley); Trial Tr. at 1566:11-1567:7 (Little)). It is also taught in the '356 Patent. (DTX-320 at CHI_CLE_0000358 ("Based on the adverse effects of EDTA, particular care should be taken when administering EDTA to patients with renal impairment, liver toxicity, tuberculosis, and impaired cardiac function."); Trial Tr. at 1567:11–25 (Little)).

One of the attorneys that prosecuted the Patents in Suit before the Patent Office testified that "[p]articular care means that you should be careful" and because the '356 Patent "talks about fatality, hypokalemia, so combining the reading, . . . that means you should not be administering EDTA." (Trial Tr. at 875:7–16 (Tsevdos)). She went on to state that the '356 Patent "says fatality. So [she's] pretty sure that that is something that is to be taken into consideration." (Trial Tr. at 875:17-20 (Tsevdos); *see also* FoF ¶ 392). Again, Aurobindo relied upon this exact disclosure from the '356 Patent to state to the Patent Office during prosecution of its own clevidipine patent application that "the use of EDTA in any such [clevidipine] formulation would be contraindicated." (PTX-864.135; Trial Tr. at 1569:11–22 (Little)). Aurobindo similarly relied upon the Ebata prior art reference (DTX-314) ("Ebata") in front of the Patent Office. Aurobindo stated that Ebata "caution[s] against the combination of EDTA . . . and a dihydropyridine calcium channel blocker such as clevidipine because both chelating agents and active drug regulate calcium ions. Thus, [as Aurobindo explained] "one skilled in the art would not have combined EDTA, or other chelating agents and clevidipine for administration to regulate blood pressure because of the uncertain interaction among them." (PTX-864.136; Trial Tr. at 1569:11–22 (Little)). As with the

'356 Patent, both the applicants of the Patents-in-Suit and Aurobindo relied upon Ebata before the USPTO to evidence the non-obviousness of EDTA with clevidipine. (Tr. at 1569:23-1570:2 (Little)). Contrary to what it stated before the Patent Office, at trial Aurobindo cited to the HPE (which is also cited in the '356 Patent) to suggest that it cautions against the administration of only disodium edetate, not all forms of EDTA. But the '356 Patent, when citing to the Handbook, does not limit its disclosure to disodium edetate. Instead, it teaches against "administering EDTA . . . to patients with . . . impaired cardiac function." (DTX-320 at 2:22–25). Prosecuting attorney Tsevdos testified that she agreed with the '356 Patent's interpretation of the Handbook, i.e., that it referred to all forms of EDTA generally. (Trial Tr. at 876:3–877:1 (Tsevdos)). Dr. Crowley conceded that such an understanding of the Handbook—that it applied to all forms of EDTA—was not unreasonable. (Trial Tr. at 1333:7–1336:4 (Crowley)).

One of Aurobindo's own product development scientists, who is also the lead inventor on the Aurobindo patent application, testified that he was aware of side effects, in particular cardiovascular side effects, when using EDTA in pharmaceutical formulations, without any limitation on the type of EDTA being used. (Trial Tr. at 261:24–262:3, 287:1–288:13, 289:19–290:11 (Barik)).

Again, Chiesi says that contrary to what Aurobindo stated before the USPTO, Aurobindo argued at trial that the disclosure regarding cardiovascular side effects would not be applicable for clevidipine because clevidipine is indicated for hypertension, and hypertension is purportedly not equivalent to impaired cardiac function. But studies of clevidipine in patients who needed cardiac surgery formed part of the basis of Cleviprex's FDA approval. (Trial Tr. at 74:18–76:22 (Zwinski); PTX-048.10, 14 (Improved Cleviprex Package Insert disclosure of Eclipse Study); PTX-053.9, 12 (Original Cleviprex Package Insert disclosure of Eclipse Study)). Dr. Crowley

agreed that a patient who needs cardiac surgery has impaired cardiac function. (Trial Tr. at 1337:15–23 (Crowley)). Dr. Crowley also had no reason to disagree that impaired cardiac function is caused by a number of things, one of which is hypertension. (Tr. at 1338:4-8 (Crowley)). Dr. Little agreed with this fact as well. (Tr. at 1643:1-20 (Little)).

Fourth, Chiesi contends that none of the references relied upon by Dr. Crowley at trial provided a motivation to use EDTA with clevidipine as an antimicrobial agent. They addressed each of the references in turn.

(a) Jones '520 Patent

Chiesi observed that the Jones '520 Patent was before the Patent Office during the prosecution of the Patents in Suit. (PTX-004.207-209 ('676 Patent File History); PTX-005.445-451 ('537 Patent File History); PTX-006.1093-1103 ('490 Patent File History)). Jones disclosed an intravenous propofol formulation containing 0.005% EDTA. (DTX-027 at claim 34; Trial Tr. at 1307:5–9 (Crowley)). During the prosecution of the '537 Patent, the applicants also submitted other references disclosing propofol formulations with 0.005% EDTA: WO 01/89474 (PTX-005.227-243), WO 99/39696 (PTX-005.635-685), and WO 2004/010941 (PTX-005.765-836). (PTX-005.216-218; PTX-005.445-451). As such, Chiesi points out that the Examiner already considered propofol and EDTA- related prior art (including the Jones '520 Patent specifically) during prosecution.

Even setting aside the fact that the Examiner already considered Jones and references like it, Chiesi introduced evidence that the drugs are distinct. Unlike clevidipine, propofol is not a calcium channel blocker and, therefore, the combination of EDTA and propofol is not subject to the same safety concerns as the combination of EDTA and clevidipine. And, unlike clevidipine, propofol is not specifically intended for use in patients with high blood pressure and/or impaired cardiac function. It is used to for anesthesia and sedation in patients. (Trial Tr. at 1571:20–24

(Little); DTX-027 at 6:3–11). In short, propofol and clevidipine are two different drugs that are not even in the same therapeutic space. (Trial Tr. at 81:17–82:11 (Zwinski); Trial Tr. at 1571:20–24, 1588:17–1589:12 (Little); Trial Tr. at 768:4–17 (Williams); Trial Tr. at 817:4–16 (Ding); Tr. at 879:25-880:14 (Tsevdos)).

(b) Thompson

According to Chiesi, Thompson teaches that the antimicrobial effectiveness of EDTA is "dependent on the bacteria as well as the medium involved." (DTX-053 at Aur_Cle- 00116401; Trial Tr. at 1571:4–13 (Little)). For this reason, a POSA would not have thought that EDTA would have had the same antimicrobial properties regardless of the context of the composition in which it was included. (Trial Tr. at 1308:2-6, 1309:6-8 (Crowley); Trial Tr. at 1572:4–1573:4 (Little)). For example, although Dr. Crowley opined that Thompson taught that EDTA was effective against 20 microorganisms, he admitted that this was "specific to the Diprivan composition." (Trial Tr. at 1309:6–8 (Crowley)). In short, neither Jones nor Thompson would have taught a POSA anything about EDTA's antimicrobial effectiveness in the context of clevidipine.

(c) ICH Guidance

To the extent Aurobindo intended to show otherwise, Chiesi maintains that the ICH Guidance (DTX-024), and its disclosure regarding ways to address specific objectionable bacteria, would not have motivated a POSA to add EDTA to clevidipine as an antimicrobial agent either. To that end, Dr. Little testified that "[t]he ICH Guidance, specifically Q6A here, is talking about harmonization of specifications for pharmaceutical products." (Trial Tr. at 1573:5-22 (Little)). That is, the ICH Guidance talks about formulations "very generally"; it "does not specifically mention emulsion formulations as being the focus. It is not about clevidipine. It's not about EDTA." (Trial Tr. at 1573:20-1574:4 (Little)). "[M]ore importantly, when you go through and you look at the parts that talk about the objectionable bacteria [referenced by Dr. Crowley] that

you're looking to determine, those are in the sections on oral dosage forms," not injectables like those claimed in the Patents-in-Suit. (Trial Tr. at 1574:5–19 (Little); DTX-024 at Aur_Cle-0006930-6932). And while "[t]here is a section on injectables," "[i]t doesn't mention determining specific objectionable bacteria in that section." (Trial Tr. at 1574:20-22 (Little); DTX-024 at Aur-Cle-0006935–6937).

(d) Chen

Chiesi next disputes the applicability of United States Patent Application No. 2005/0186230 to Andrew Chen ("Chen") (DTX-023). Like Jones, Chen was before the Patent Office during prosecution of the Patents in Suit. (PTX-004.167-187 ('676 Patent File History); PTX-005.391-401 ('537 Patent File History); PTX-006.77-95 ('490 Patent File History)). As such, the Examiner already considered Chen. Again, even setting aside that fact, the formulations discussed in Chen are elemenes, which Dr. Little described as "a specific class of chemical compounds that are typically derived from plants" that were "being explored for anticancer treatment." (Trial Tr. at 1575:7–17 (Little)). Chen "doesn't mention clevidipine," and while "[i]t does mention EDTA . . . it talks about EDTA to potentially prevent microbial growth, but there is no specific degree of microbial growth that's discussed in [Chen] that is acceptable, and there is no data." (Trial Tr. at 1575:18–22 (Little)). Consequently, Aurobindo says Chen "at best is similar to the propofol references, because it talks about EDTA being in there with a completely different drug," and since there is no data, a POSA would not give Chen much, if any, weight. (Trial Tr. at 1576:2–7 (Little)). Chiesi also noted that Dr. Crowley did not dispute this point.

(e) FDA Inactive Ingredient Database

Chiesi elicited testimony from both parties' experts that the FDA Inactive Ingredient Database does not identify EDTA's function in the products it discloses. (Trial Tr. at 1277:5–18, 1338:10-1339:3 (Crowley); Trial Tr. at 1578:25-1579:21 (Little)). In fact, Dr. Crowley expressly

clarified this point during his direct examination, testifying: "I should note the database doesn't ascribe a functionality. So I don't know if it was an antimicrobial in those 50 products. It could be there as an antioxidant to simply address oxidation reactions, for example. So I can't ascribe functionality . . . ." (Trial Tr. at 1277:5-17 (Crowley); *see also* Trial Tr. at 1355:10-15 (Dr. Crowley testifying on redirect that EDTA has "long been used for their predominantly antioxidant properties" and as a chelator only, not also as an antimicrobial agent) (Crowley)). Dr. Little agreed that functions for EDTA other than as an antimicrobial agent were more likely. (Trial Tr. at 1579:3–21 ("Again, EDTA is a very commonly used preservative for a completely different reason. So I don't think that somebody looking at that list is going to look at it and think, okay, well, in each of those cases it's being used as an antimicrobial resistance agent. It wouldn't even make sense if that's the case because when you look at some of those, there wouldn't be a need for that.") (Little)).

(f) Intralipid

Other than Diprivan, Cheisi maintains that there is no evidence that any of the other products with Intralipid were formulated with EDTA, and other drugs listed on DDX-15 (in addition to Original Cleviprex) were formulated without EDTA after Diprivan+EDTA was approved in 1996. Thus, although Diprivan and Original Cleviprex were both formulated with Intralipid, this common feature would not have provided a reason for a POSA to add EDTA to clevidipine as an antimicrobial agent.

(2) No Motivation to Include Oleic Acid

Chiesi also disputes Aurobindo's assertion that a POSA would have been motivated to add oleic acid in the claimed amount to clevidipine and EDTA as a stabilizing co-emulsifier and arrive at either of claim 7 of the '537 Patent or claim 6 of the '490. First, Dr. Crowley admitted on cross-examination that a POSA generally would not have expected instability in a clevidipine+EDTA

emulsion, largely because EDTA did not destabilize the Diprivan emulsion (Trial Tr. at 1343:23–1344:10 (Crowley)). Dr. Little cited the apparent inconsistency that if Dr. Crowley believed that as POSA "would know that it would be stable when you add [EDTA] to a formulation, then you wouldn't need to add a co-emulsifier. It wouldn't be something that you would think to add." (Trial Tr. at 1580:3–315 (Little)).

Second, the presence of soybean oil in Original Cleviprex would not have provided a motivation to choose oleic acid, given the many alternatives for stabilization. Chiesi accuses Dr. Crowley of using hindsight to focus solely on the oleic acid component of soybean oil instead of looking at the full field of potential co-emulsifiers, including palmitic acid and stearic acid, other components of soybean oil. According to Dr. Little, a POSA would not have focused on just oleic acid, but would have considered other co-emulsifiers as well (assuming a POSA even believed one was needed), because "[t]here are numerous other ways in which an oil-in-water emulsion could be stabilized." (Trial Tr. at 1632:15–24 (Little)). Moreover, Dr. Little opined that a POSA would have understood that the oleic acid associated with soybean was a different form than what is claimed. It is generally understood that the oleic acid in soybean oil is esterified, not free oleic acid. Testimony from fact witnesses was consistent on this point. (Trial Tr. at 1009:4–14 (Ms. Caivano testifying that soybean oil contains esterified oleic acid); Trial Tr. at 150:15-151:2 (Dr. Motheram testifying in response to cross-examination that soybean oil contains oleic acid in the ester form)).

Dr. Crowley relied upon various prior art to argue why a POSA would have purportedly been motivated to add oleic acid to clevidipine and EDTA as a stabilizing co-emulsifier. However, none of the references mention clevidipine or EDTA. (Trial Tr. at 1586:25–1587:11 (Little)). Dr. Little opined that "[j]ust because you have something [i.e., oleic acid] that works in another

formulation you wouldn't assume that it would work in a clevidipine formulation with EDTA." (Tr. at 1587:12-17 (Little)). As support, Dr. Little cited a finding from the European Patent Office that Chiesi introduced from a related patent application that the "solution [of adding oleic acid] could not be derived and extrapolated from documents of the prior art which, while disclosing oleic acid, either they don't comprise an active agent or if, yes, it's a totally different drug." (Trial Tr. at 1587:18-1588:14 (Little)).

Finally, Chiesi points out that two of the references cited by Dr. Crowley, Yamaguchi and Levy (DTX-041), were already considered by the Patent Office during prosecution of the Patents in Suit. (PTX-005.2545 ('537 Patent File History, citing Yamaguchi); PTX-006.1070 ('490 Patent File History, citing Yamaguchi and Levy); *see also* Tr. at 1295:24–1296:9 (Crowley)). In fact, the applicants overcame a rejection based on alleged oleic acid prior art during prosecution. (PTX-006.1525-1532, 1880-1881 ('490 Patent File History)).

d) *No Reasonable Expectation of Success*

For similar reasons to why it believes a POSA would not be motivated to arrive at the claimed inventions, Chiesi contends a POSA would not have a reasonable expectation of success in doing so.[15] There was no evidence in the prior art that EDTA would work as an antimicrobial agent with clevidipine. Neither Jones '520 nor Thompson disclosed clevidipine and EDTA together. These references involved propofol rather than clevidipine. Chiesi argues that Aurobindo failed to explain how their teachings would apply to clevidipine, particularly given that Dr. Crowley admitted that that there were many variables that could affect microbial growth in a pharmaceutical formulation, and that he was not asked to provide opinions about the possible

[15] More accurately, Chiesi asserts that Aurobindo failed to show that either the prior art would motivate a POSA to arrive at that claimed inventions or provide a POSA with a reasonable expectation of success in doing so.

sources of microbial contamination in this case.[16] (Trial Tr. at 1349:5-22 (Crowley)). He also admitted that a POSA, reviewing the references, would not have thought that adding EDTA to Original Cleviprex would adversely affect the stability of the emulsion. (Trial Tr. at 1253:20–1254:6, 1343:11–21 (Crowley)). Chiesi maintains that the FDA Briefing Document could not have provided a reasonable expectation of success because it was an internal confidential document, drafted by the inventors in hindsight after invention. Chiesi repeats similar arguments with respect to the addition of oleic acid.

e) No Evidence of Secondary Considerations

The Court notes that the parties introduced no evidence at trial of the presence or absence of secondary considerations that might support the nonobviousness of the claimed inventions.

4. Findings as to the Scope and Content of the Prior Art

The Court has already found that the date of invention of the Patents in Suit occurred no later than April 1, 2009. In this section, the Court discusses the key prior art references in this matter.

a) Original Cleviprex

At the time of inventions, Original Cleviprex had been recently approved in December 2008 and constituted prior art. It contained the same active ingredient and many of the same excipients as the claimed inventions. *See* PTX-053 (Original Cleviprex Package Insert, dated 2008)). It did not, however, contain EDTA or oleic acid. *Id*.

[16] Chiesi separately asserts Aurobindo erred with respect to claim 8 of the '676 Patent and claim 6 of the '490 Patent. For a prior art teaching of the 24-hour microbial resistance limitation of those claims, Aurobindo relies on Jones '520 Patent, but Jones does not disclose that level of microbial resistance, even for propofol. (Trial Tr. at 1310:11-1311:17 (Crowley) (admitting on cross examination that Jones provided testing and data for only "four, not the five," standard USP microorganisms discussed in the Patents-in- Suit and that he "misspoke" when he testified otherwise)).

b) The FDA Briefing Document and Product Development Section of the Improved Cleviprex sNDA

The FDA Briefing Document and Product Development section of the Improved Cleviprex sNDA were filed with the FDA in support of the application for its approval. Chiesi asserts that the documents were confidential, and no evidence has been presented to indicate that they were either published or "known" by others in the United States. They are therefore, as Chiesi argues, not prior art. *See, e.g., Onyx Therapeutics, Inc. v. Cipla Ltd*., Civ. No. 16-988, 2020 WL 2214443, at *20 (D. Del. May 4, 2020) (holding that a patentee's NDA is a confidential document that does not constitute prior art); *Asterias Biotherapeutics, Inc. v. Viacyte, Inc.*, Civ. No. 12-04813, 2014 WL 93903, at *7 (N.D. Cal. Jan. 9, 2014) (holding that the patentee's internal, "confidential information is not relevant to the knowledge of a person of ordinary skill in the art")). Still, Aurobindo asserts at various points in its post-trial briefing that statements made by the inventors in these documents remain relevant as admissions with respect to the motivation and reasonable expectation of success a POSA might have had in arriving at the claimed invention. For example, Aurobindo argues that:

> 548. Here, all the claims being asserted by Chiesi against Aurobindo are obvious based on the prior art of record along with the admissions as to the knowledge of a POSA in the FDA Briefing Document, the Product Development section of the NDA, the specification of the patents, and the file histories.
>
> 652. The FDA Briefing Document (PTX-0069) and the Product Development section of the NDA for reformulated Cleviprex® (PTX-800) contain admissions as to the understanding of a POSA in relation to the common use of both EDTA as an antimicrobial agent in oil-in-water emulsions, and oleic acid as a stabilizer in such injectable oil-in water emulsions at the time the Briefing Document was drafted which would have to been before April 1, 2009.

(Aurobindo Proposed Findings of Fact and Conclusions of Law, ¶¶ 548, 652). Aurobindo proffers no authority to support its attempt to apply statements from these confidential documents in this

manner. As pointed out by Chiesi, at least one court has concluded this would be improper. *See Cephalon Inc. v. Slayback Pharma Ltd.*, 456 F. Supp. 3d 594, 612 (D. Del. 2020); *aff'd* 856 F. App'x 309 (Fed. Cir. 2021) (Declining to rely on FDA submissions, in part because "conclusions drawn from a patentee's disclosures to the FDA risk being distorted by hind-sight bias.") This is consistent with the uniform recognition that viewing an invention from an inventor's perspective is impermissible hindsight. *See Otsuka*, 678 F.3d at 1296 ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the [POSA] would have followed, as evidenced by the pertinent prior art."); *see also Life Techs.*, 224 F.3d at 1325 ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."). As the party seeking to establish invalidity, it was Aurobindo's burden to articulate a basis for applying the regulatory documents in the way that it seeks. Insofar as it failed to do so, and because the Court finds that it would invite improper hindsight, the Court declines to consider Aurobindo's arguments that rely upon the FDA Briefing Document or the Improved Cleviprex Product Development Report. [17]

c) The Jones '520 Patent

The Jones '520 Patent was issued on February 3, 1998. (DTX-027) It was considered by the Patent Office during the prosecution of the Patents in Suit. It disclosed "a sterile pharmaceutical composition for parenteral administration which comprises an oil-in-water emulsion in which propofol… is emulsified with water and stabilized by means of a surfactant, and further comprises an amount of edetate sufficient to prevent significant growth of

[17] The Court notes a superficial asymmetry in the law in this respect. An ANDA applicant's product development report—while not prior art because it too is confidential—is sometimes cited by plaintiffs for evidence of admissions with respect to secondary considerations under the *Graham* factual inquiries, such as commercial success or failure of others. The relevant distinction between citing a product development report from an NDA and one from an ANDA is essentially the same one the Court relies upon here: risk of hindsight. It is the inventors (or others working in conjunction with the inventors) who prepare an NDA development report to summarize their invention. Using that report as part of an obviousness analysis is applying hindsight, which is impermissible.

microorganisms for at least 24 hours." (DTX-027 4:38–44). It described the most preferable amount of EDTA for its formulation as 1.5 x 10^{-4} moles/liter, which corresponds to 0.005% w/v EDTA in the pharmaceutical formulation of propofol. (DTX-027 5:5–7). It also noted that "EDTA is not regarded as a broad spectrum antimicrobial agent." (DTX-027 at 4:22–37; Trial Tr. at 1310:11-21 (Crowley); Trial Tr. at 1562:25–1563:17 (Little)).

d) Thompson

"The Recent Development of Propofol (Diprivan®)" by Karen A. Thompson and David Goodale was published in 2000. (DTX-053). It is prior art that was not considered by the Patent Office during the prosecution of the Patents in Suit. Thompson described the development of Diprivan and the investigation of the additive EDTA as an antimicrobial to an oil-in-water emulsion of propofol. (DTX-053 Aur_Cle-00116400). In this regard it is comparable to the Jones '520 Patent. Thompson noted that clusters of infections were observed with original Diprivan and the CDC implicated "extrinsic microbial contamination of propofol through improper use of the drug." An additive was therefore sought with "the ability to suppress the growth of microorganisms after extrinsic contamination without compromising the clinical efficacy of the propofol emulsion." It also observed that the FDA "required that the chosen additive be capable of retarding the growth of microorganisms to not greater than 10-fold within 24 hours after extrinsic microbial contamination equivalent to 'touch contamination.'" It disclosed that EDTA met the requirements and had itself been previously used clinically in an aqueous intravenous solution to treat other conditions. It stated that, as an additive in a number of pharmaceutical products and at 0.005% concentration in the propofol emulsion, EDTA was found to be effective against 20 microorganisms, although it also disclosed that EDTA "should not be considered a complete antimicrobial agent because its action is dependent on the bacterium as well as the medium involved."

e) The Oleic Acid References: Yamaguchi, Levy

"Physicochemical Characterization of Parenteral Lipid Emulsion: Influence of Cosurfactants on Flocculation and Coalescence" by Yamaguchi ("Yamaguchi") was published in 1995. (PTX.0069.161–165). "Characterization of diazepam submicron emulsion interface: role of oleic acid" by Levy ("Levy") was published in 1994. Both of these references are prior art. Yamaguchi studied the use of co-surfactants to stabilize lipid emulsions, albeit without active pharmaceutical ingredients. It disclosed that oleic acid had been observed to stabilize lipid emulsions by preventing flocculation and coalescence. Levy disclosed the use of oleic acid to stabilize a diazepam emulsion and discussed the effect of oleic acid on the emulsion's zeta potential to do so. Both of these references were considered by the Patent Office during prosecution of the Patents in Suit.

5. Findings as to the Differences Between the Claims and the Prior art

Aurobindo contends the prior art above renders the claimed inventions obvious. The main prior references pertain to: Original Cleviprex without either EDTA or oleic acid; use of EDTA in emulsions (ones that do not contain clevidipine); and use of oleic acid as a co-surfactant in emulsions (that also do not contain clevidipine). Aurobindo asserts that a POSA, considering these references and other art in the record in combination, would have been motivated to arrive at the claimed inventions with a reasonable expectation of success. Chiesi counters that the references would not motivate a POSA, that Aurobindo's obviousness defense is based on impermissible hindsight, and that a POSA would not have had a reasonable expectation of success.

(1) A POSA Would Not Have Been Motivated to Arrive at the Claimed Inventions

To begin, it is undisputed in this case that formulating oil-in-water emulsions is a complex and unpredictable science. Aurobindo expressly admitted as much in its July 2021 statements to

the Patent Office while prosecuting its own patent application directed to a clevidipine+EDTA product. (PTX-864.134 (Aurobindo asserting to the USPTO that "[oil-in-water] emulsion and emulsion products are very complex from formulation and stability perspective and not very predictable," and that the "[p]resent composition is not ordinary parenteral composition but it is O/W emulsion and emulsion products are very complex from formulation and stability perspective"); Trial Tr. at 1376:6–17 (Akhave) (confirming same)). The Federal Circuit has held that "evidence showing unpredictability in the art" suggests "that one of ordinary skill would not have been motivated to combine the references with a reasonable expectation of success." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354 (Fed. Cir. 2017).

Against that backdrop, the Court rejects Aurobindo's argument that a POSA would have appreciated that the Original Cleviprex formulation posed a problem to be addressed. In relevant part, Aurobindo attempts to rely upon the Background of Invention section of the patents in suit, which states:

> Accordingly, there exists a need for a stable clevidipine emulsion formulation that is resistant to microbial growth, thereby diminishing the risk of microbial contamination in patients and providing greater ease in handling. Such a formulation would also result in cost savings to the health care providers and patients in decreasing the wastage of clevidipine and reducing the time-consuming efforts involved with manipulation and replacement of vials containing the drug.

('676 Patent 1:48–55). It is true that statements in a Background of Invention section that recognize a pre-existing motivation in the art can be deemed admissions by the inventors. *See, e.g.*, *Medpointe Healthcare Inc. v. Hi-Tech Pharmacal Co.*, 115 F. App'x 76, 80 (Fed. Cir. 2004) ("[T]he inventors . . . admitted in the Background of Invention section of their patent that at the time of invention it was at least somewhat accepted that '[a]ntitussives, antihistamines, and

decongestants in the form of their tannate salts are very desirable because such salts are generally stable and may be combined in such form without any untoward side effects.' . . . This statement from the . . . patent appears to acknowledge the presence of an existing motivation to undertake the salt conversion that the district court evidently deemed missing from the record evidence.") In this case, however, the Court interprets the inventors' statements in their Background of Invention section as articulating their own motivation for pursuing the invention rather than acknowledging a known, existing motivation in the art. The Court therefore finds that this portion of the Background of Invention section does not represent an admission by the inventors and that applying their statements would therefore constitute impermissible hindsight.

The Court also finds that a POSA would not have been motivated to modify Original Cleviprex based on the prior art's teachings with respect to Diprivan (propofol), as Aurobindo claims. First, as the parties' experts agreed at trial, a preservative was added to original Diprivan to address infections that had been reported by clinicians. However, as the parties' experts also agreed, there were no similar reports made with respect to Original Cleviprex. Second, the modifications to Diprivan were made over a decade earlier. Had Diprivan presented the sort of broad motivation to modify emulsions as Aurobindo claims, it follows that it would have motivated the inclusion of EDTA in Original Cleviprex. Third, the Patent Office already considered—and issued the asserted claims over—the Jones '520 Patent and its disclosure of Diprivan emulsions containing EDTA, reducing the persuasive weight the Court assigns Jones's teachings. Fourth, the Court credits the unrebutted and thorough testimony of Dr. Little, together with statements from both the Jones and Thompson references, to the effect that a POSA would not have looked to EDTA as a preservative because it was not known at the time to be a particularly good antimicrobial agent. (Trial Tr. at 1550:19–1551:9 (Little); 1562:11–24 (same), 1551:10-13

(EDTA "was specifically taught to not be a broad-spectrum antimicrobial agent and it was specifically taught to be used with other [antimicrobial agents], not by itself.") (Little)); see also (DTX-027 at 4:22-37; Tr. at 1310:11-21 (Crowley); Tr. at 1562:25–1563:17 (Little); (DTX-053 at Aur_Cle-00116401; Tr. at 1310:3-10 (Crowley); Tr. at 1562:25-1563:3, 1563:8-24 (Little)). Testimony from Dr. Crowley supports the notion that a POSA would not have looked to EDTA insofar as he conceded that effectiveness against a wide spectrum of bacteria would have been a "major criteria" for a POSA's selection. (Trial Tr. at 1307:21–1308:1 (Crowley)).

For these reasons, the Court finds that Aurobindo has not demonstrated by clear and convincing evidence that a POSA would have been motivated to add EDTA to clevidipine as an antimicrobial agent. The Court concludes on this basis that the asserted claims, each of which incorporate an EDTA limitation, are not obvious over the cited prior art.[18]

G. Unenforceability

In support of its unenforceability arguments, Aurobindo proffered as an expert at trial Dr. Dr. Nancy Linck, Ph.D., J.D. Dr. Linck is an adjunct law professor at University of San Diego and a former Solicitor for the Patent Office and former administrative patent judge. Prior to that, she prosecuted patent applications before the Patent Office for several years as both a private practitioner with a firm and as in-house counsel for Monsanto. Since 2016, she has been the principal of NJ Linck Consulting, frequently providing testimony with respect to inequitable conduct. Dr. Linck was accepted by the Court as an expert in procedure and practice with the Patent Office. In rebuttal, Chiesi presented Robert L. Stoll, J.D. Mr. Stoll was the former

[18] Given its conclusion with respect to the lack Aurobindo's evidence of a motivation to add EDTA, the Court does not consider the remaining disputed limitations of the asserted claims, e.g, the concentration of the EDTA, or the inclusion, and concentration, of oleic acid. The Court also does not reach Chiesi's arguments that a POSA would not be motivated to add EDTA because it is contraindicated for use in combination with clevidipine as a calcium channel blocker.

Commission of Patents at the Patent Office, where he worked for 29 years, including as a patent examiner for 12 years. (Trial Tr. 1437:4–25 (Stoll)). He is currently a partner at Faegre Drinker Biddle & Reath LLP where he serves as deputy chair of the intellectual property group. (Trial Tr. 1440:8–14 (Stoll)). The Court accepted Mr. Stoll as an expert in the field of Patent Office practice and procedure. (Trial Tr. 1441:11–21). Chiesi also offered technical testimony from Dr. Little in support of its rebuttal.

1. Inequitable Conduct/Unclean Hands[19]

Under its Rules, the Patent Office imposes a duty to disclose information material to patentability. 37 C.F.R. § 1.56. The duty applies to "[e]ach individual associated with the filing and prosecution of a patent application." *Id.* More specifically, the duty falls upon "[e]ach inventor named in the application," "[e]ach attorney or agent who prepares or prosecutes the application," as well as "[e]very other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, the applicant, an assignee, or anyone to whom there is an obligation to assign the application." *Id.* at § 1.56(c).

Inequitable conduct is an equitable defense to patent infringement. *Therasense Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1285 (Fed. Cir. 2011) (en banc). The Federal Circuit has set a very high bar for the accused infringer who seeks to defend against a charge of patent infringement based on inequitable conduct: "[t]o prove inequitable conduct, [it] must show by clear and convincing evidence that the patent applicant (1) misrepresented or omitted information material to patentability, and (2) did so with specific intent to mislead or deceive the PTO." *In re*

[19] Plaintiff filed two motions pertaining to unenforceability that the parties agreed in a subsequent letter submission (ECF No. 376) had been rendered moot: Plaintiff's Bench Brief Regarding Attorneys Accused of Misconduct (ECF No. 309) and Plaintiff's Motion to Preclude Inequitable Conduct Allegations (ECF No. 310). The Court will therefore deny these motions as moot.

Rosuvastatin Calcium Patent Litig., 703 F.3d 511, 519 (Fed. Cir. 2012) (citing *Therasense*, 649 F.3d at 1287. "Materiality and intent must be separately established." *Id.*

The materiality required to establish inequitable conduct is "but-for" materiality. *Therasense,* 649 F.3d. at 1287. But-for materiality is established if the Patent Office would not have issued the claim but for the omitted or misrepresented information. *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1334 (Fed. Cir. 2012) (quoting *Therasense*, 649 F.3d at 1291). A reference is not "but-for" material if it is "merely cumulative" to information already considered by the examiner. *Larson Mfg. Co. of S. Dakota v. Aluminart Prod. Ltd.*, 559 F.3d 1317, 1327 (Fed. Cir. 2009). A reference is cumulative when it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1574–75 (Fed. Cir. 1997). Accordingly, under Rule 1.56, the Patent Office relieves an applicant of the duty to disclose prior art that is merely cumulative to art already before the Patent Office. *See* 37 C.F.R. § 1.56(b).

An exception to the but-for materiality requirement exists for affirmative egregious misconduct materiality" requirement, examples of which include extreme misdeeds, such as filing unmistakably false affidavits, suborning perjury, bribing witnesses, and actively suppressing evidence. *Therasense,* 649 F.3d at 1292–93. This exception deals with "deliberately planned and carefully executed schemes to defraud the PTO and the courts." *Id.* at 1292 (citation and internal quotation marks omitted).

To establish specific intent to deceive the Patent Office, "clear and convincing evidence must show that the applicant made a deliberate decision to withhold a known material reference." *Id*. at 1290. The party asserting must prove by clear and convincing evidence that the accused: (1) knew of the information, (2) knew that it was material, and then (3) made a deliberate decision to

withhold it. *Id*. Mere failure to disclose material information—even if tantamount to gross negligence—is insufficient. *Id*. (citing *Kingsdown Med. Cons., Ltd. v. Hollister Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988)). "Proving that the applicant knew of a reference, should have known of its materiality, and decided not to submit it to the PTO does not prove specific intent to deceive." *Id*. (citation omitted).

Deceptive intent can be inferred from circumstantial evidence, but to meet the clear and convincing evidence standard, the "inference must not only be based on sufficient evidence and be reasonable in light of that evidence, but it must also be the single most reasonable inference able to be drawn from the evidence." *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008). "[T]he evidence must be sufficient to require a finding of deceitful intent in the light of all the circumstances." *Therasense*, 649 F.3d at 1290 (citation and quotation marks omitted). "Hence, when there are multiple reasonable inferences that may be drawn, intent to deceive cannot be found." *Id.* at 1290–91 (citation omitted).

a) Aurobindo's Evidence and Arguments

In a nutshell, Aurobindo first argues that inequitable conduct was perpetrated when the inventors argued to the FDA in 2009 that adding EDTA and oleic acid to Original Cleviprex would be safe, but later argued to the Patent Office from 2010–2013 that a POSA would consider it unsafe. Specifically, a portion of the FDA Briefing Document devoted to the description of the CMC development activities for Improved Cleviprex included the following section:

> 4.2 IDENTIFICATION OF PRESERVATIVE CANDIDATES
>
> As a first step, the scientific literature was reviewed and potential preservatives were assessed against the following criteria:
> - Safety
> - Preservative effectiveness
> - Use in approved injectable products for intravenous administration

> • Preservative physicochemical stability under alkaline conditions
> • Potential impact on emulsion and drug substance physicochemical stability
>
> As a result of these considerations, disodium edetate, benzyl alcohol, sodium citrate and sodium ascorbate were selected as candidates for initial screening and evaluation.

(FDA Briefing Document at 14, PTX-0069.14). In a later section of the same document titled "Safety of Proposed Product," it made the following relevant representations:

> 5.1 SAFETY OF 0.03% ADDITIONAL OLEIC ACID AND 0.005% EDTA
>
> …
>
> EDTA is also a commonly used pharmaceutical excipient and is generally recognized as safe. From the perspective of IV administration, literature reviews were conducted as part of MDCO's comprehensive nonclinical and clinical safety assessments of EDTA as a preservative for use in Cleviprex at the level of 0.005%.
>
> The nonclinical safety assessment concludes that "Based on available nonclinical and clinical data, safety margins for human exposure to EDTA at doses and dose rates associated with clinical administration of the [new] preserved IV formulation of clevidipine are large, typically 100- to over 1000-fold.", and that 0.005% EDTA in Cleviprex poses no safety risk to humans [Final Nonclinical Study Report. Duddy SK, 2009].
>
> This finding is consistent with the clinical literature which indicates that EDTA, administered intravenously as Calcium Disodium Versenate (for the treatment of lead intoxication) can be safely administered to adult and pediatric patients using doses up to 1000 mg/m^2/day for 5 days.
>
> More relevant comparisons include the use of EDTA (0.005%) to retard microbial growth in intravenous propofol, which is a lipid-based emulsion vehicle. The propofol literature includes multiple references describing EDTA as having no effect or no significant effect in critically ill adult or pediatric patients [Abraham et al, 2000; Barr et al, 2000; Cohen et al, 2001; Herr et al, 2000; Wahr et al, 2000]. Additional information supporting this position includes the FDA's reviews of US NDA 19-627/S-027 [NDA 19-627/S-027, 2006] in which reviewers concluded that 0.005% EDTA had no effect or no meaningful effect on propofol safety or pharmacokinetics.

> 5.2 SAFETY OF PROPOSED DRUG PRODUCT
> Collectively, the addition of 0.03% oleic acid and 0.005% EDTA poses no new safety risks.

(FDA Briefing Document at 30, PTX-0069.30).

Aurobindo observed that FDA Briefing Document also included an external report from Dr. Steven Duddy, titled "Review of Nonclinical Data and Safety Assessment of EDTA as a Preservative in Intravenous Formulations of Clevidipine." (PTX-0069.64–78.) Dr. Duddy was a "safety pharmacology consultant" who conducted "an extensive literature review." (Trial Tr. 763:7–8,17–21 (Williams)). In the course of describing the purpose for preparing his report, Dr., he makes the following statement:

> Since there are approved IV products containing similar or higher concentrations of EDTA that are safely used in clinical practice, no issues are anticipated. However, adverse events associated with IV administration of very high doses of EDTA are well documented, and occur primarily in the context of chelation therapy for metal intoxication or hypercalcemia. Such instances of EDTA toxicity are due principally to induction of hypocalcemia and, presumptively, to disruption of trace metal homeostasis due to the higher relative affinity of EDTA for metals such as zinc (Zn) than sodium (Na) or calcium (Ca).

(Duddy Report at 4–5, PTX0069.67–68).

Dr. Duddy ultimately concluded his report as follows:

> Based on available nonclinical and clinical data, safety margins for human exposure to EDTA at doses and dose rates associated with clinical administration of the preserved IV formulation of clevidipine are large, typically 100- to over 1000-fold. Thus, the proposed clinical uses of the preserved formulation of clevidipine would not be expected to result in adverse effects.

(Duddy Report at 13, PTX-0069.76). According to Aurobindo, these statements in the FDA Briefing Document and the Duddy Report were made to the FDA in order to obtain approval of

Improved Cleviprex via sNDA and thereby avoid running clinical trials. (Trial Tr. 1050:3–9 (Linck)).

Aurobindo contrasts these representations to the FDA with positions taken before the Patent Office while prosecuting the applications for the Patents in Suit beginning 18 months later. To begin, Aurobindo claims the arguments themselves were inconsistent. Moreover, it says, none of the five references FDA propofol references—Abraham et al, 2000; Barr et al, 2000; Cohen et al, 2001; Herr et al, 2000; Wahr et al, 2000—cited in the FDA Briefing document were submitted to the Patent Office when the initial provisional patent application was filed. Nor were they shared at various points in the prosecution of the Patents in Suit when Aurobindo says the inventors made contradictory arguments to the Patent Office that EDTA was taught away from use in intravenous preparations (Prosecution of the '667 Patent, PTX-0004.334) and that a POSA would be taught away from the combination of EDTA with clevidipine because it was a calcium channel blocker (Prosecution of the '537 Patent, PTX-0005.380). Aurobindo observed that the record showed that the inventors did, however, submit various references in support of their positions, notably the Cumberland Pharmaceutical citizen petition that sought to stop generic manufacturers from making the original product on the basis that EDTA was removed for safety reasons. (PTX-0004.334). The petition was supplied even though it had already been denied by the FDA on the basis that EDTA use in propofol had been shown to be safe. (Trial Tr. 1111:2–1112:2 (Linck)). A Bayer Leukine reference was also provided to the Patent Office for a teaching away from use of EDTA in intravenous preparations. (PTX-0004.334).

(1) Materiality

In summary fashion, Dr. Linck opined that the actions above were material to patentability insofar as a reasonable examiner assigned to the '537 and '676 patents would not have allowed the patents to issue but-for the inconsistent arguments made to the Patent Office and the withheld

references. (Trial Tr. 1125:2–18 (Linck)). Aurobindo did not provide testimony from a technical expert in support of its but-for materiality assertions.

(2) Specific Intent

With respect to the specific intent to deceive element of inequitable conduct Aurobindo introduced no direct evidence. Rather, it cited to the conduct above as what it characterizes as a multiplicity of mis-actions in this case that indicate suspiciously selective memories of Dr. Motheram, Dr. Williams, the in-house attorney and multiple outside prosecuting counsel.[20] Aurobindo urges that under these circumstances, the single most reasonable inference to be drawn from the evidence is a specific intent to deceive the Patent Office by the inventors and their in-house counsel.

b) Chiesi's Evidence and Arguments

At trial, Chiesi advanced four reasons why Aurobindo's inequitable conduct accusations fail for lack of materiality: (1) Chiesi placed all of Aurobindo's allegations and the underlying references before the Examiner during prosecution of the '490 Patent and the Examiner issued the '490 Patent, indicating that the arguments and undisclosed references are not material; (2) interpreted properly, the statements made to the Patent Office and the FDA were not actually inconsistent; (3) other information about the safety of EDTA and clevidipine was before the Patent Office during prosecution of the '676 and '537 Patents; and (4) Aurobindo's own statements to the Patent Office while prosecuting its own patent application contradict its inequitable conduct allegations here.

[20] The Court notes that Aurobindo explicitly stated at trial that it was making "no accusations against the lawyers. We are saying that… what actions they did is attributable to the applicant because they were acting on behalf of the applicants." (Trial Tr. 469:9–12 (Moore)).

(1) Allowance of the '490 Patent

Chiesi introduced evidence showing that the FDA Submissions, as well as Aurobindo's inequitable conduct allegations concerning them, were considered by the Patent Examiner (who was the same Examiner that reviewed the '676 Patent), who then allowed the claims of the '490 Patent over that information. (Trial Tr. at 1443:20–1444:1 (Stoll); PTX-006.1450-2004)). The same Examiner examined both the '676 Patent and the '490 Patent. (Tr. at 1443:15-19 (Stoll)). Mr. Stoll opined that the claims allowed in the '490 Patent are similar to the other Patents in Suit insofar as all of them related to clevidipine with EDTA and oleic acid. (Trial Tr. 1443:23–1444:12 (Stoll)). According to Stoll, this is further supported by the Examiner's own finding that the claims are sufficiently similar as to be patentably indistinct. (Trial Tr. at 1444:2-1445:6 (Stoll); see, e.g., PTX-0006.1428-1432).

Chiesi recounted in detail how it disclosed the inequitable conduct allegations to the Patent Office. In May 2021, the applicants of the '490 Patent submitted to the Examiner the parties' pleadings from this litigation which detailed Aurobindo's bases for its inequitable conduct and unclean hands claims, including with respect to the FDA Submissions for the '676 and '537 Patents. The applicants also submitted to the Examiner through IDS submissions on May 4 and May 5, 2021 the FDA Briefing Document (including the Duddy Report), the Duddy Report separately, and the FDA Propofol References. (Trial Tr. at 1445:8–1447:20 (Stoll); PTX-0006.1450-1498, 0006.1533-1535, 0006.1720-1723, 0006.1901-1902, 0006.1897-1898).

The Examiner reviewed and considered the documents submitted with the May 4 and 5 IDS submissions as evidenced by the electronic signature in those documents as provided for by MPEP § 609. (Trial Tr. at 1446:20-1447:20 (Stoll); Trial Tr. at 1139:24-1140:5 (Linck); PTX-0006.1901-1902, 0006.1897-1898, *see also* MPEP § 609.01 ("[I]nserting on each page of reference citations the phrase 'All references considered except where lined through' along withthe

examiner's electronic initials.")). Pursuant to MPEP § 609.05(b), the Examiner's electronic signature provided in accordance with MPEP § 609.01 "provides a clear record of which citations have been considered by the [USPTO]." Dr. Linck admitted that under Patent Office practice and procedure, an examiner's electronic initials or signature on an IDS creates a presumption that the references listed have been reviewed by the Examiner. (Tr. at 1139:3–1140:5 (Linck)).

When providing to the Examiner the FDA Submissions and Aurobindo's corresponding inequitable conduct and unclean hands allegations, the applicants' attorney specifically drew the Examiner's attention to Aurobindo's claims asserted against Plaintiffs in this litigation. (Trial Tr. at 1445:22-1446:19 (Stoll); PTX-0006.1525-1526; 0006.1450-1498 (Exhibit 1)). During an interview on May 27, 2021, the applicants' attorney discussed the present litigation concerning the validity of the parent patents (i.e., '676 and '537 Patents) and the FDA Briefing Documents. The Examiner stated that he would review the IDS submissions filed on May 4 and 5. (Tr. at 1447:21-1448:17 (Stoll); PTX-0006.1878). On May 6, 2021, the Examiner signed the May 4 and 5 IDS submissions, indicating that the references listed therein had been reviewed and considered. (PTX-006.1896–1898; PTX-006.1901–1902; Trial Tr. at 1447:7–20 (Stoll); Trial Tr. at 1139:24–1140:5 (Linck)). On June 4, 2021, the Examiner issued a Notice of Allowance for the claims of the '490 Patent. (PTX-0006.1880-1888). In the Notice of Allowance, the Examiner stated that he "re-weighed all the evidence of record." (PTX-0006.1886). Mr. Stoll testified that "re-weighed all the evidence of record" means that the Examiner "looked at all of the different office actions that had occurred, all of the arguments, all of the references, and determined that the claims were still patentable." (Tr. at 1449:1-9 (Stoll)). Dr. Linck agreed, testifying that she "ha[d] no reason to doubt that [the Examiner] reviewed all the evidence" before issuing the June 4 Notice of Allowance. (Trial Tr. at 1143:18-1144:13 (Linck)).

Mr. Stoll opined that the issuance of the June 4 Notice of Allowance by Examiner Arnold demonstrated that the FDA Submissions were not "but-for" material to the patentability of the claims of the '490 Patent, and accordingly, were not "but-for" material to the patentability of the related claims of the '676 and '537 Patents. (Trial Tr. at 1449:10–13 (Stoll)).

On June 11, 2021, applicants' attorney submitted another IDS to the Examiner that disclosed Aurobindo's revised inequitable conduct and unclean hands allegations, which included the original allegations concerning the FDA Submissions as well as new allegations pertaining to the prosecution of the '490 Patent (i.e., regarding infectious unenforceability, the Motheram Declaration, and the Caivano Declaration). (Trial Tr. at 1449:14–1450:5 (Stoll); Trial Tr. at 1144:14–1146:2 (Linck); PTX-006.1944–1962). The revised allegations submitted to the Examiner during the prosecution of the '490 Patent contained allegations corresponding to Counts III.A-F and Count IV in the September 13 Answer. (PTX-0006.1916-1972). The Examiner considered that information and again allowed the claims of the '490 Patent, stating that the June 11 submission "did not change the previous determination of patentability." (PTX-006.2000; 006.2004; Tr. at 1450:6-19 (Stoll)). Again, Dr. Linck did not have any reason to doubt the Examiner's conclusion in response to the June 11 submission. (Trial Tr. at 1146:22–1147:11 (Linck)).

For these reasons, Chiesi asserts that the fact that the Examiner of the '490 Patent found that the submitted information had no impact on the patentability of the claims of the '490 Patent, therefore demonstrates that it is not "butfor" material to the patentability of the '676 and '537 Patents.

(2) Statements to FDA and the Patent Office Were Consistent

Chiesi separately maintains that statements made to the Patent Office and FDA regarding the use of EDTA with clevidipine are actually consistent given that they were made to the two

agencies concerning two different timeframes and perspectives. Mr. Stoll testified that, under Patent Office practice and procedure, the statements made to the Patent Office were related to the legal standards for patentability (i.e., what was known at the time of invention to a POSA), while the statements made to the FDA were made after the invention and with knowledge of all of the development work that went into Improved Cleviprex. (Tr. at 1458:5-1459:17 (Stoll)). Dr. Little offered consistent testimony. (Tr. at 1600:9–1601:24 (Little)).

According to Chiesi, the prosecution histories of the '676 and '537 Patents demonstrate that statements made to the USPTO were made from the perspective of a POSA at the time the invention was made. For example, during the prosecution of the '676 and '537 Patents, the applicants stated in a response to an office action that "at the time the invention was made," a POSA would not have considered EDTA to be an ideal choice to use in formulation with clevidipine (a calcium channel blocker) "because of its potential effects on emulsion stability and particularly because of its role on chelating calcium ions." (PTX-0004.278; PTX0004.281; PTX-0005.205-06; Tr. at 1548:14-19 (Little); Tr. at 1458:23-1459:11 (Stoll)). Later in that same document, the applicants pointed to prior art references (i.e., Ebata, Luchoski, and Ptasienski) in support of their position regarding what one skilled in the art at the time of invention would think, stating that: These references taken together caution against the combination of EDTA, or other chelating agents, and a dihydropyridine calcium channel blocker because both chelating agents and active drugs regulate calcium ions. Thus, one skilled in the art would not have combined EDTA, or other chelating agents, and clevidipine for administration to regulate blood pressure because of the uncertain interactions among them. (PTX-004.278-79; PTX-005.205-06). Dr. Motheram testified that the concern he had when developing the new formulation with clevidipine (i.e., at the time of the invention), as a formulator, was the reaction between EDTA (a chelating

agent) and clevidipine (a calcium channel blocker). (Tr. at 111:11-112:1 (Motheram)). He said he explained this concern from a formulation perspective to the Examiner during the prosecution of the '676 Patent. (Trial Tr. at 140:20-24 (Motheram)). He indicated that he even had that concern with formulations he worked on containing propofol—contemporaneous with the filing date of the '676 and '537 Patents. (Tr. at 112:2-115:11 (Motheram); PTX-802 at 5:67-6:3, 1:51-56; PTX-803 at 2:24-37). Chiesi cites Aurobindo's technical expert, Dr. Crowley, who credited Dr. Motheram's concern by testifying that "I don't think that's an unreasonable concern. And I heard Dr. Motheram state that, and I take him at his word." (Tr. at 1333:7-1336:4 (Crowley)). Dr. Little further elaborated on how the potential safety issues with EDTA would have been a concern to a POSA. (Trial Tr. at 1566:4–1568:7; PTX-071.4; PTX-181.2 (Little)).[21]

Chiesi contends that the applicants' arguments to the Patent Office were made from the perspective of a POSA at the time of invention and who, critically, would not have had knowledge of the invention. (Trial Tr. at 1458:5-1459:17 (Stoll); Tr. at 1600:9-1602:24 (Little)). Dr. Little testified that, without knowledge of the invention, a POSA would not have had all the information about the formulation being claimed. A POSA would not have known what the final formulation would be or whether it would be safe, effective, stable and/or work in the way it needs to. (Tr. at 1600:9-1602:24 (Little)). In short, the statements made in the FDA Briefing Document (and in the Duddy Report) were made with knowledge of the invention, after it had already been made.

In Dr. Little's view, Aurobindo's argument is also incorrectly based upon the position that the FDA Briefing Document does not contain any non-public information and testing data for

[21] In fact, as discussed further, infra, Aurobindo expressed these same safety concerns with EDTA to the Patent Office during prosecution of its own clevidipine, EDTA, and oleic acid patent application. (Tr. at 1568:8-1570:2 (Little); PTX-819.3; PTX-864.135-136). Moreover, Aurobindo's own scientist, who is also the lead inventor on the Aurobindo patent application, conceded that he was aware of side effects, in particular cardiovascular side effects, when using EDTA in pharmaceutical formulations. (Trial Tr. at 261:24-262:3, 287:1-288:13, 289:19-290:11 (Barik)).

Improved Cleviprex. (Trial Tr. at 1598:5-1599:11 (Little)). The FDA Briefing Document includes information regarding the proposed formulation of Improved Cleviprex with EDTA and oleic acid, administration information, manufacturing information, as well as visual appearance testing, stability testing, and microbial resistance testing data for Improved Cleviprex. (Tr. at 1597:3-20, 1598:5-1599:11 (Little); PTX-0069.14-31)). Table 6 of the FDA Briefing Document also includes the proposed formulation for Improved Cleviprex, specifying the exact amounts of EDTA and oleic acid used in the proposed formulation. (PTX-0069.23). Neither Dr. Linck, nor Dr. Crowley, testified about this information disclosed in the FDA Briefing Document. Section 5 of the FDA Briefing Document discussed information relevant to the safety of the specific Improved Cleviprex and its dosing. The FDA Briefing Document further included a request for a bioequivalence waiver. (Trial Tr. at 1597:3-20 (Little); PTX-0069.14-31)). As Aurobindo's witness agreed, a biowaiver "refers to an instance in which the FDA allows the [] applicant to submit dissolution and/or disintegration data, in lieu of performing a bioequivalence study, in order to demonstrate bioequivalence of its [] product." (Trial Tr. at 567:7- 568:6 (Ghan)). Therefore, the request for a biowaiver does not relate to the safety of the product.

Chiesi disputed Aurobindo's and Dr. Linck's assertions that the safety conclusions set forth in Section 5 of the FDA Briefing Document, and the statements therein that rely on the Duddy Report, are contradictory to the arguments made to the USPTO. (Tr. at 1060:11-24; 1061:14-1065:9 (Linck)). According to Chiesi, the FDA Briefing Document and the Duddy Report are not prior art, and Aurobindo admits this. Instead, as Dr. Linck testified, the corroborated date of invention is April 1, 2009, and the Duddy Report itself corroborates this date. (Tr. at 1135:5-1136:13 (Linck)). She also testified that, by the time of the Duddy Report, a formulation containing clevidipine, EDTA, and oleic acid was in existence. *Id.* Dr. Little agreed. (Tr. at 1597:3-

1599:14 (Little)). Dr. Motheram and Dr. Williams also confirmed that Improved Cleviprex had been formulated and made by the time of the FDA Briefing Document, including the Duddy Report. (Tr. at 125:13-126:20 (Motheram); Tr. at 779:15-19 (Williams)). In addition, the analysis from the Duddy Report does not appear anywhere in the prior art, and neither of Aurobindo's experts (Drs. Linck or Crowley) did the analysis that Dr. Duddy conducted based on what was available in the prior art. (Tr. at 1599:23-1600:8 (Little)).

Chiesi notes that other statements in the Duddy Report to the FDA are consistent with the statements made by applicants to the Patent Office. Similar to the statements made to the Patent Office, the Duddy Report also expressly states that there was a general concern with EDTA toxicity: "Such instances of EDTA toxicity are due principally to induction of hypocalcemia . . . ." (PTX-0069.68; Trial Tr. at 784:3-785:7 (Williams)).

(3) The Applicants Put Other Information About the Safety of EDTA and Clevidipine Before the Patent Office During Prosecution of the '676 and '537 Patents

As a separate point, Chiesi argued that information about the safety of EDTA with clevidipine after the time of invention was disclosed to the Patent Office during the prosecution of the '676 and '537 Patents. For example, during prosecution of the '676 Patent, in-house counsel and Dr. Motheram together identified the Improved Cleviprex 2011 package insert to the Examiner and discussed the history of selecting an antimicrobial agent in clevidipine compositions with the Examiners at an interview held on June 20, 2013. (PTX-004.205; Tr. at 129:21-131:10 (Motheram); Tr. at 1149:7-12, 1150:14-22; 1151:9-11 (Linck)). The Improved Cleviprex 2011 package insert was submitted to the Examiners in both the prosecutions of the '676 and '537 Patents in Information Disclosure Statements. (PTX-004.318; PTX-005.404; PTX-004.241-257; PTX-005.326-342). The Examiner in each instance signed the IDS, indicating that the references were considered and reviewed. (; Tr. at 1457:1-3 (Stoll); Tr. at 1139:24-1140:5, 1149:3-6 (Linck)).

The Improved Cleviprex 2011 package insert illustrates that the Improved Cleviprex formulation with EDTA was safe and FDA-approved. (PTX-005.326-342; Tr. at 1456:12-25 (Stoll); Tr. at 1602:6-1603:8 (Little)). The FDA approval letter for Improved Cleviprex was also submitted during the prosecution of the '537 Patent. (PTX-005.404; PTX-005.362-64; Tr. at 1457:22-25 (Stoll)). The Examiner signed the IDS with that letter indicating that he considered and reviewed it. The letter request for a bioequivalence waiver for Improved Cleviprex was also submitted during the prosecution of the '537 Patent. (PTX-005.2429-2431). The Examiner signed the IDS with that letter indicating that he considered and reviewed it. (PTX-005.2545). Chiesi cites this as an indication that the applicants and their attorneys were forthright with the Patent Office regarding the safety of the use of EDTA and clevidipine in Improved Cleviprex, and that the Patent Office had considered and reviewed the information during the prosecution of the '676 and '537 Patents.

(4) Aurobindo's Own Statements to the Patent Office While Prosecuting Its Own Patent Application Contradict Its Inequitable Conduct Allegations in this Case

In an unlikely turn of events, Chiesi introduced evidence that Aurobindo itself told the Patent Office that the amount of EDTA in Improved Cleviprex was unsafe when applying for its patent, but then told the FDA that the amount of EDTA in its ANDA Products was safe based on a biowaiver using Improved Cleviprex as the comparator. (Trial Tr. at 1603:11-1606:10 (Little)). In fact, Aurobindo based the purported novelty of its patent application on the same safety concerns with the combination of EDTA and clevidipine due to EDTA's chelating effect and potential contraindication with clevidipine—even after the issuance of the '676 and '537 Patents and after the FDA approved Improved Cleviprex. (Tr. 1568:12-1569:10, 1603:11-1604:16 (Little); PTX-819.3; PTX-864.135-136). In its U.S. patent application published on October 8, 2020, Aurobindo states:

> Intravenous formulations using disodium EDTA can lead to [a] decline in concentration of calcium . . . . A rapid decline in blood calcium can lead tomuscle spasm. It can cause severe hypocalcemia, brachiopods, bronchial spasms, seizures and even apnea. Effects on the cardiovascular system. . . can occur in severe ventricular fibrillation.
>
> Hence, there is still a need to design pharmaceutical composition[s] of clevidipine that have prolonged stability, efficacy and reduced side effects. Inventors of the present invention have endeavored to develop such formulations that are also economical and commercially viable while having none or lower concentration of antimicrobial agent [EDTA]. . . .

(PTX-819.3). Thus, even in 2017 (when Aurobindo's patent application was filed), Aurobindo argued to the Patent Office that the art taught away from using of EDTA in combination with clevidipine due to EDTA's calcium reduction effect and effect on the cardiovascular system. This is both after the inventions in the Patents in Suit were made and after the approval of Improved Cleviprex by the FDA. (Trial Tr. at 1568:8-1569:10 (Little)).

Aurobindo repeated its arguments when the USPTO rejected its application, and again asserted teaching away arguments based on EDTA in an August 10, 2021 submission (dated July 28 2021) while this suit was pending. Those arguments are the same ones that Aurobindo alleges in this case were intentionally misleading when made by the applicants during prosecution of the '676 and '537 Patents. (Trial Tr. 1569:11-1570:2, 1603:22-1604:16 (Little); Tr. at 1375:1-1377:14 (Akhave)). In its post-trial submissions, Chiesi submitted a side-by-side comparison of examples that the Court duplicates below.

Chiesi USPTO Arguments Accused of Inequitable Conduct in this Litigation	Arguments Aurobindo and Mr. Jay Akhave Made to Patent Office
"[Ebata, Ptasienski, and Luchoski] taken together caution against the combination of EDTA, or other chelating agents, and a dihydropyridine calcium channel blocker because both chelating agents and active drugs regulate calcium ions. Thus, one of skill in the art would not have combined EDTA, or other chelating agents, and clevidipine for administration to regulate blood pressure because of the uncertain interactions among them.'" PTX-004.279; Tr. at 1082:21-1083:24 (Linck).	"Ebata et al., suggests caution against the combination of EDTA, or other chelating agents, and a dihydropyridine calcium channel blocker such as clevidipine because both chelating agents and active drug regulate calcium ions. Thus, one skilled in the art would not have combined EDTA, or other chelating agents and clevidipine for administration to regulate blood pressure because of the uncertain interaction among them." PTX-864.136.
"Applicant is providing US Patent 8,148,356 for the examiner's review. In there, particularly, at column 2, line 23-25, the reference importantly indicates that intravenous drugs with EDTA should not be administered to patients with 'renal impairment, liver toxicity, tuberculosis and impaired, cardiac function.' Clevidipine is used when a patient has impaired cardiac function, and as such, the use of EDTA in any such formulation would be contraindicated." PTX-004.334; Tr. at 1158:5-17, 1161:4-6 (Linck).	"It is mentioned in the literature (US8148356; Column 2, line 22-35; see below) that, intravenous drugs with EDTA should be used with special care to patients with 'renal impairment, liver toxicity, tuberculosis and impaired cardiac function.' Clevidipine is used when a patient has impaired cardiac function (Reduction in Blood pressure), and as such, the use of EDTA in any such formulation would be contraindicated." PTX-864.135.

(Chiesi PFOF ¶ 454). By way of summary on this issue, Chiesi elicited testimony from Aurobindo's own technical expert on the nature of Aurobindo's inconsistent representations to the Patent Office, stating that "I want the record to state I didn't know about it. I had nothing to do with it. And it's indefensible." (Trial Tr. 1336:6–1337:13 (Crowley)).

c) Findings as to But-for Materiality

Having reviewed the extensive record before it, and for the reasons set forth below, the Court finds that Aurobindo failed to prove that the applicants misrepresented or omitted

information to the USPTO during the prosecution of the '676 and '537 Patents that was "but-for" material to the patentability of those patents.

Dr. Linck opined only summarily that the conduct presented by Aurobindo was but-for material. In contrast, the Examiner's allowance of the '490 Patent claims is compelling evidence that the information Aurobindo cites here is not material at all, much less but-for material. It is clear from the record that the Chiesi made every effort to disclose Aurobindo's allegations and the FDA submissions and that Examiner reviewed them. Dr. Linck's attempt to distinguish the prosecution of the '490 Patent was credibly rebutted by Mr. Stoll's emphasis as to the significance of an Examiner's acknowledgement of his review of the prior art together with the Examiner's own explicit statement that he had "re-weighed all the evidence of record" as part of his review. Dr. Linck conceded that she had no reason to doubt the Examiner's review. Likewise, the Court found credible Mr. Stoll's opinion (corroborated by the Examiner's observation) that the claims of the '490 Patent and the claims of the other Patents in Suit are sufficiently similar to make relevant the Examiner's conclusion regarding the patentability of the 490 Patent.

For these reasons the Court finds that Aurobindo has failed to demonstrate that the arguments made during prosecution of '676 and '537 Patents, or the references not disclosed, are

but-for material. [22] In light of its finding with respect to materiality, the Court concludes that Aurobindo has failed to establish inequitable conduct or unclean hands on that basis.[23]

VI. CONCLUSION

For the reasons set forth above, the Court concludes that: the Patents in Suit are infringed; the Patents in Suit are not invalid; and the Patents in Suit are not unenforceable. An appropriate Order will follow.

Date: **August 16, 2022**

s/ Zahid N. Quraishi
ZAHID N. QURAISHI
UNITED STATES DISTRICT JUDGE

[22] Chiesi also filed a Motion to Dismiss Aurobindo's Counterclaim III (Declaratory Judgment of Unenforceability based on Inequitable Conduct) and Counterclaim IV (Declaratory Judgment of Unenforceability based on Unclean Hands and to Partially Strike Aurobindo's Second Affirmative Defense (Invalidity/Unenforceability). (ECF No. 167). The parties submitted briefs at ECF Nos. 168, 176, and 178. Given that the Motion was briefed shortly before trial, the Court reserved its decision for trial. As a preliminary matter, the Court notes that a portion of the Motion to Dismiss is moot insofar as it pertained to Aurobindo's allegation that Chiesi submitted an inaccurate translation to the Patent Office of a German fact sheet for Lipvenoes® 20%, and Aurobindo appears to have waived its position by introducing no evidence on that issue at trial. The remainder of Chiesi's Motion to Dismiss is premised on the notion that the Examiner's decision to issue the '490 Patent after reviewing Aurobindo's accusations of inequitable conduct meant that Aurobindo's position could not meet the required but-for standard for materiality. Having the reviewed the parties' briefs and Aurobindo's relevant pleadings, the Court agrees that Aurobindo's pleadings are scant. Still, the Court declines to grant Chiesi's motion to dismiss in favor of considering the trial record, particularly the parties' respective evidence with regard to how close the claims of the '490 Patent are to the claims of the '676 and '537 Patent and therefore the relevance of the Examiner's decision to issue the '490 Patent.

[23] Given its conclusion as to materiality, the Court does not reach Aurobindo's showing regarding specific intent to deceive the Patent Office beyond recognizing that Aurobindo introduced no direct evidence of such intent. For the same reason, the Court denies as moot Chiesi's motion seeking to preclude demonstratives and testimony from Dr. Linck as to legal conclusions or specific intent of individuals or institutions. (ECF No. 320). For the same reason again, the Court also denies as moot the applicable portion of Chiesi's motion (ECF No. 341) seeking to strike Dr. Linck's testimony.